Dietary and lifestyle modification in metabolic syndrome: a review of randomized control trials in different population groups

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Abstract

The emergence of modernization coupled with sedentary lifestyle has resulted in the shift from the prevalence of diseases only due to under nutrition, to those caused by over nutrition. The augmentation of non-communicable diseases, thus, imposes double burden of disease, impeding the health of a nation. This upsurge has led to increase in prevalence and incidence of Metabolic syndrome which is a cluster of inter-related factors characterized by high fasting blood glucose, increased level of triglycerides, low levels of high density cholesterol, elevated blood pressure and abdominal obesity. The best way to combat this syndrome is to reduce the atherosclerotic risk, which can be carried out by modification in the diet and lifestyle – the first line of treatment of the syndrome. Thus, the present review was undertaken to understand the already existing as well as the current scenario specifically regarding the dietary and lifestyle interventions being carried out to overcome Metabolic syndrome. Of the randomized control trials reviewed, all except one reported improvement in Metabolic syndrome following intervention in diet and/or lifestyle modification either in certain components or overall syndrome within a period of 2 weeks–1 year. These interventions to alter diet and lifestyle focus on weight reduction, promotion of regular physical activity, reduction of substance abuse, effectiveness of specific food items along with regulation of genes and various inflammatory markers. They have the potential to succeed only if they are executed early, and thus, offer enough evidence to develop appropriate public policies. However, the issue that is of utmost significance is of sustainability and compliance, which eventually decides the long-term success or failure of an intervention.

Keywords

Metabolic syndrome; Lifestyle; Intervention studies

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Introduction

With the advent of modernization, subsequent development of new facilities has led to sedentary lifestyle and consumption of high caloric diet, leading to an imbalance between the energy intake and energy expenditure [1,2]. This has led to rise in obesity which leads to other co-morbidities such as hypertension, insulin resistance, dyslipidemia, and diabetes eventually leading to Metabolic Syndrome (MetS) which acts as a precursor to cardiovascular disease (CVD) [1,2]. With continuing under nutrition, and escalation in over nutrition, there is double burden of diseases (communicable and non-communicable) hovering on nations especially the developing countries which do not have adequate resources [3,4]. The global prevalence of chronic diseases is on rise in the developing countries with a share of 60% alone [5]. They will be accountable for three quarters of deaths worldwide by 2020 with a share of 71% due to CVD and 70% due to diabetes mellitus (DM) in the developing countries [6]. India will continue to hold its position as the highest DM patients' country in the world [7]. This increase in the prevalence of the non-communicable diseases (NCDs) currently as well as the high projected prevalence in the future is apprehensive. Strategizing public health policies and intervention programs is the top priority and need of the hour. Though pharmacological approach is one way of treating this problem, changes in the diet and lifestyle are the foremost hurdles that are needed to be crossed [8]. Therefore, the main objective of undertaking this review was to assess the effectiveness of dietary and lifestyle interventions in different population groups in overcoming MetS.

Methodology

In this article, we have reviewed the existing research regarding diet and lifestyle in treating or reducing MetS. We reviewed recent and past literature using Medline, PubMed (National Library of Medicine, Bethesda, MD, USA), Cochrane Library, Science Direct and Google Scholar databases. The keywords that were used included metabolic syndrome, diet, lifestyle, Mediterranean diet, intervention, insulin resistance, obesity, non- communicable diseases, hypertension, HDL, triglycerides, inflammation, genetics, CRP. Published randomized control trials (RCTs) on the effect of dietary and lifestyle interventions on MetS, which have been listed in the above mentioned databases from 2004 till 2012, have been included in this review.

Metabolic syndrome

Terminology and diagnostic criteria

The interrelationship between obesity, type 2 DM and hypertension includes hyperinsulineamia as its essential feature [9], which led to Reaven's hypothesis that clustering of insulin resistance with glucose intolerance, hypertension, and dyslipidemia leads to a unique condition known as MetS or Syndrome X [10,11]. It is a cluster of interrelated factors characterized by high fasting blood glucose, increased level of triglycerides, low levels of high density lipoprotein (HDL), elevated blood pressure and abdominal obesity [12]. However the criteria for defining the syndrome are various (Table I).

Irrespective of the varying criteria proposed by different definitions, the prevalence of MetS is on the rise in both western as well as the Asian countries [1,13-15]. Increment in the proportion of diagnosed individuals can be related to increase in age as well as in body mass index (BMI) [16]. Not only the western societies, but also the developing countries are now getting engulfed in the burden of this problem. This

Diagnostic criteria	Expert group/Organization						
	WHO, 1998	EGIR, 1999	NCEP: ATPIII, 2001	AACE, 2003	AHA/NHLBI, 2005	IDF, 2005	Consensus definition, 2005*
IFG	>100 mg/dl	110 mg/dl or greater	110 mg/dl or greater	Impaired glucose tolerance	100 mg/dl or greater	100 mg/dl or greater	100 mg/dl or greater
WC		M ≥ 94 cm, W ≥ 80 cm	M > 102 cm, W > 88 cm		M ≥ 102 cm, W ≥88 cm	BMI > 30 kg/m² or elevated WC (according to population and country-specific definitions)#	Elevated WC (according to population and country-specific definitions)#
WHR	M > 0.9, W > 0.85						
BMI	> 30 kg/m²			≥ 30 kg/m²			
TG	TG ≥ 150 mg/dl and/or HDL-C: M < 40 mg/dl W < 50 mg/dl	≥ 150 mg/dl and/or HDL-C: < 39 mg/dl in M or W	≥ 150 mg/dl	TG ≥ 150 mg/dl and/or HDL-C: M < 40 mg/dl, W < 50 mg/dl	≥ 150 mg/dl	≥ 150 mg/dl	150 mg/dl or greater
HDL- C			M < 40 mg/dl, W < 50 mg/dl		M < 40 mg/dl, W < 50 mg/dl	M < 40 mg/dl, W < 50 mg/dl	M < 40 mg/dl, W < 50 mg/dl
BP	≥ 140/90 mmHg	≥ 140/90 mmHg	≥ 130/85 mmHg	≥ 130/85 mmHg	≥ 130/85 mmHg	≥ 130/85 mmHg	≥ 130/85 mmHg
Any other	-	-	-	-	-	-	Microalbuminuria ≥ 20 µg/min or ≥ 30 mg/g

Table I. Diagnostic criteria for Metabolic Syndrome

AACE = American Association of Clinical Endocrinology; AHA/NHLBI = American Heart Association/ National Heart, Lung, and Blood Institute; BMI = Body Mass Index; EGIR = European Group for the Study of Insulin Resistance; IDF = International Diabetes Federation; NCEP ATPIII = National Cholesterol Education Program Adult TreatMt Panel III; WC = waist circumference; WHR = Waist Hip ratio; WHO = World Health Organization
M = M; W = W
*Incorporating IDF and AHA/NHLBI definitions; IFG = impaired fasting glucose; TG = triglycerides; HDL-C = High Density Lipoprotein Cholesterol; BP = blood pressure
Waist circumference: for Europeans, > 94 cm in M and > 80 cm in W; and for South Asians, Chinese, and Japanese, > 90 cm in M and > 80 cm in W. 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

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 [17-20]. Abdominal obesity [21-23], insulin resistance [10,11], along with physical inactivity [22,24], aging [25], hormonal imbalance [26], and atherogenic diet (a diet rich in saturated fat and cholesterol) are some factors that can exacerbate the risk for developing MetS, and consequently CVD [12].

Prevalence and risk factors

MetS is present worldwide, continuing to rise, with many countries now facing its burden [27]. According to the Framingham study, 25% of new cases of CVD are accounted by MetS. Prevalence of MetS is on the rise in the developing countries (affecting nearly ¼th of the populations), including India.

CVD accounted for 39% of deaths in India, attributing it to be the leading cause of mortality in 2005 [27]. Not only urban but rural populations are also being affected by it [28-30]. Prevalence of MetS is widespread, as can be observed through literature available over the years. There is not only an increasing trend in the South Asians residing in the Indian subcontinent but also in migrants [31], with an estimated prevalence of 20-25% [32]. The contributory factors for MetS (Table II) are age [33-37], sex [36,38-40], region [36,38,41,42], income [43-46], Adult Treatment Panel III (ATPIII) or International

Ref.	Design & country	Sample	Finding(s)
[34]	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) • Prevalence 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)
[35]	Cross-sectional, Australia	N=5,850 of which 4,060 had biochemical examination	• Prevalence IDF criteria: 22.8 (26.4% in men, 15.7% in women) • Prevalence ATPIII criteria: 15.0% (19.4% in men, 14.4% in women)
[36]	Cross-sectional Jaipur, India (Urban)	N=1,091 (532 men; 559 women) adults >20 years	• Prevalence ATPIII criteria: 345 (31.6%) subjects – males 122 (22.9%); females 223 (39.9%) (p<0.001) • Increase in prevalence with age (p<0.05)
[37]	Prospective, Case-Control U.S.A	N= cases 32,826 women 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: CRP = 3.99, P <0.001)
[38]	Cross-sectional Chandigarh, India (Urban)	Adults aged 18 years and above	• Prevalence IDF criteria: 287 adults (47.4%) – females 171 (59.6%); males 116 (40.4%) • Prevalence ATPIII criteria: 233 adults (38.5%) – females 141 (44.8%); males 116 (39.5%)
[41]	Cross-sectional Toto tribe, Bhutia tribe	N=258 (Toto); 310 (Bhutia)	• Prevalence ATPIII criteria: 30-50% in Bhutia tribe; 4-9% in Toto tribe • MetS not necessarily related to modernization
[43]	Cross-sectional London, U.K (High, Middle, Lower income)	N=1,509 women; 4,090 men (aged 45.2-68.9 years)	• Inverse association of own and household income and wealth with MetS (P<0.001). • Increased prevalence (WHO criteria) in men than women (wealthiest: 12.0 and 5.7%; poorest: 23.6 and 20.1%)
[44]	Cross-sectional France, Europe	N=1,695 men; 1,664 women, (aged 35-64 years)	• Prevalence ATPIII criteria: 390 (23.0%) men; 381 (16.9%) women • Inverse association of household income with MetS (P<0.004) in women (Sex-specific increase)
[46]	Cross-sectional London, U.K (Income-wise stratification)	N=4978 men; 2035 women (aged 39-63 years)	• Inverse association between obesity, fibrinogen and MetS, and socioeconomic status
[48]	Cross-sectional Zulia, Venezuela	N=3108 men and women (aged ≥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 MS
[49]	Cross-sectional Muscat, Oman	N=1419 adults (aged ≥20 years)	• Age adjusted prevalence ATPIII criteria: 21.0%; men 19.5%, women 23.0% (p=0.236)
[50]	Cross-sectional Pan-India (Industrial population)	N= 19,973 for questionnaire survey; 10,442 biochemical testing (aged 20-69 years)	• Prevalence ATPIII criteria: 26.6% (men 20.9%; women 36.3%) • Prevalence IDF criteria: 35.4% (men 29.4%; women 46.1%)

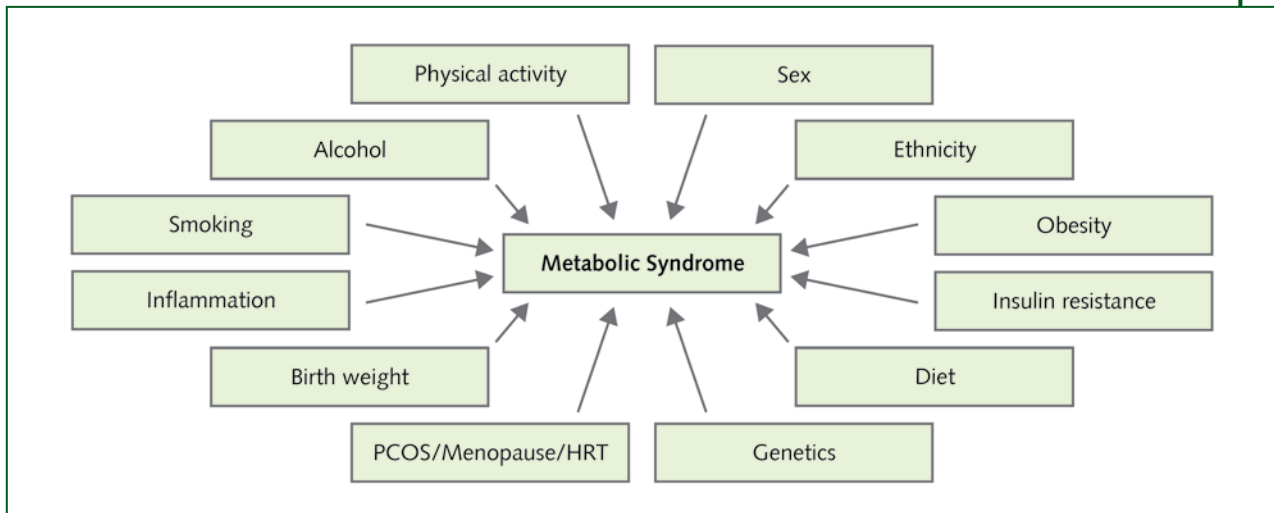**Table II.** Prevalence of Metabolic Syndrome

Figure 1. Risk factors for Metabolic Syndrome [10,12,21,22,25,26,56,57]

HRT = Hormone Replacement Therapy; PCOS = Poly Cystic Ovary Syndrome

Diabetes Federation (IDF) criteria [17,47-49] and occupation [50,51]. In light of the evidence provided in Table II, it is clear that there exists an inverse relationship between income and MetS in developed countries [43,44,46]; however, the situation is reversed in the developing countries where the prevalence increases with the rise in socioeconomic status [38]. This can be attributed to the fact that in developing countries, as the income increases, more amount of the income is spent on fats and sugars; while in the developed countries, those with the lower income prefer to buy foods rich in fats and sugar as they are much cheaper than other food items. 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 [52,53] is essential. MetS is a challenging condition as it is not a discrete entity but consists of multitude of risk factors (Figure 1). The risk varies in an individual depending on the aggregation of metabolic and non-metabolic risk factors [54]. According to the American Heart Association (AHA) statement [55], atherogenic dyslipidemia, elevated blood pressure, and elevated plasma glucose are the most familiar risk factors. Other factors include abdominal obesity [21-23], insulin resistance [10,11], along with physical inactivity [22,24], aging [25], hormonal imbalance [26], and atherogenic diet [12]. Relationship of MetS with sex, age, degree of obesity and socio-economic status has also been confirmed [56,57]. Ethnicity [25,58,59], smoking [60,61,62], alcohol consumption [63-66], inflammation [67,68,37], genetic predisposition [69,70], low birth weight [71,72], polycystic ovary syndrome (PCOS), menopause, and hormone replacement therapy (HRT) [73] have also shown their association with the syndrome. A solitary factor cannot purport to augmentation 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 [27].

Treatment of Metabolic Syndrome

Pharmacological treatment

According to AHA [55], the targeted treatment for the syndrome underlines the fact that the foremost goal is to reduce the atherosclerotic risk. This involves directing attention at the major risk factors so

that the treatment is offered to the patients' relative to their risk. The first line of intervention is however, the lifestyle therapies whether the risk is long or short term. To achieve maximum benefit, weight reduction through diet modification and increased physical activity results in risk reduction concurrently. Drug/pharmacological therapy isn't syndrome specific but risk factor specified [55]. Drugs such as antihypertensive for controlling blood pressure, aspirin for those with a greater risk (more than 10% or 10 year risk) of developing the disease, and statins, fibrates and niacin for dyslipidemias are suggested in extreme cases where diet and lifestyle modification is not enough alone. However, maintenance of blood glucose levels with haemoglobin A1$_C$ level of less than 7.0% has been the key recommendation [55]. Nonetheless, the foundation of treatment for MetS is diet and lifestyle modification.

Dietary modification

Modernization in the field of agriculture has led to changes in the diet which alongside a sedentary lifestyle has contributed to increased consumption of diets rich in fat and cholesterol leading to an overall positive energy balance [74]. Therefore, poor diet is an important component of the syndrome that needs to be targeted for its reduction and treatment. The efficacy of Mediterranean diet (MeD) on MetS has been observed through many studies [75-79]. The Mediterranean Dietary pattern typically emphasizes fruits, cooked vegetables and legumes, grains (whole, not refined) and, in moderation, wine, nuts, fish and dairy products, particularly yogurt and cheese. It is a food pattern that has the potential of improving health and quality of life in people who adhere to it appropriately characterizing a way of life and culture [80]. Specifically, each component of Mediterranean dietary pattern has its own significance that holds a key in obviating MetS. Various dietary interventions have confirmed its role in MetS management (Table III), where they have shown significant weight loss, improvement in the MetS components [75,81], improvement in body composition and cardio-metabolic fitness [82], increase in long chain N3 poly unsaturated fatty acids [79] and decrease in high sensitive C-reactive protein (hs-CRP) and insulin resistance [83].

A cross-sectional study with the participants (n=808 adults with high CVD risk) of the PREDIMED trial was conducted to understand the relationship between MeD and MetS. Negative association of the syndrome with high MeD score (≥9 points) was observed (p<0.001; OR=0.44) with specific components conferring conclusive benefits like olive oil, legumes and red wine [84]. Following this, the PREDIMED study investigators compared the effect of 2 interventions using MeD with a low fat diet on MetS with 1 year clinical trial [85]. MeD diet + 1 l/wk of virgin olive oil, MeD diet + 30 g/day of mixed nuts and advice on low fat diet (control) was given, wherein MetS was defined using ATPIII criteria. After adjustment for age, sex, weight changes and baseline obesity status, the odds ratio (OR) for MetS decline was more for the nuts group (OR=1.7) than for the virgin olive oil group (OR=1.3), substantiating the importance of MeD diet as a useful tool in MetS management. Similarly, women diagnosed with MetS in Korea (n=52; mean age, 62.7 ± 9.0 years) were subjected to a therapeutic lifestyle management program for 6 months. It included health monitoring, counselling, health education, exercise, and dieting as its components alongside measuring health related Quality of Life (QOL) index and metabolic risk factors at baseline, 3, 6 and 12 months. The program exhibited significant reductions in body weight (p<0.001), waist circumference (WC) (p<0.001), general (p<0.001) and mental health (p=0.027), and vitality (p=0.008); with decrement in body weight and WC even sustaining after intervention. Another ongoing trial in Spain is being carried out to lessen the incidence of MetS, which is apparently on the rise [86]. The reduction of the metabolic syndrome in Navarra-Spain (RESMENA-S) study is a randomized prospective parallel design (n=50) encompassing personalized weight loss (30% energy restriction) diet, with a macronutrient distribution (carbohydrate/fat/protein) of 40/30/30, high meal frequency (7/day), low glycemic index/load and high antioxidant capacity as well as a high adherence to the MeD aimed to lower the incidence of the syndrome [86].

Ref.	Country	Sample	Intervention	Finding(s)
[75]	Spain	N=45 sedentary adults (50-66 years)	Two groups: (a) hypocaloric, normoproteic MeD; and (b) the same diet plus periodized moderate-to-high intensity training (MeDE) for 12 weeks	• Significant weight loss and improvement in MetS components was achieved with hypocaloric, normoproteic Mediterranean diet ($p<0.05$) • More significant weight loss was achieved with the combination of MeD and moderate intensity physical activity post 12 weeks compared to MeD alone ($p<0.05$)
[76]	U.S.A	Women; n=44 control; n=45 intervention	Control (Mediterranean-style low-glycemic-load diet) vs. intervention (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
[79]	Germany	N=101 adults	Med diet group + 100 hrs of education (n=48) vs. written advice only group (n=53)	• 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 in the intervention group • No change in the markers of inflammation like hs-CRP, fibrinogen, fasting insulin, homocysteine, serum lipids and plasma fatty acids
[81]	Houston, Texas, USA	N=81 (22 men)	12 week, 3 groups: 0, 8, or 16 fluid ounces of low sodium vegetable juice	• More weight loss, high consumption of Vitamin C, potassium, and dietary vegetables was observed in the juice drinking group ($p<0.05$) compared to those only on diet counselling
[82]	Whyalla, South Australia	N=153 obese adults with MetS	Randomized to intervention or control for 16 weeks. INT group: lifestyle program which provided a curriculum and practical strategies on 1) dietary and Physical Activity information based on national guidelines, 2) behavioural self-management tools, 3) food-label reading, supermarkets tour and cooking, 4) exercise sessions, and 5) peer-group support	• Significant improvement observed in body composition ($p<0.01$), physical and cardio-metabolic fitness ($p<0.01$) with minimally prescriptive lifestyle intervention program
[83]	Naples, Italy	N = 180 adults (99 men and 81 women) with MetS (ATPIII criteria): 90 in control and 90 in intervention group	Patients in the intervention group were instructed to follow a Mediterranean-style diet and received detailed advice about how to increase daily consumption of whole grains, fruits, vegetables, nuts, and olive oil; patients in the control group followed a prudent diet (carbohydrates, 50-60%; proteins, 15-20%; total fat, <30%)	• 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
[134]	U.S.A	N = 54 normal weight young women; 18 to 31 years	Two year exercise intervention. Three sessions of resistance exercise plus 60 minutes of jumping rope per week or a control group for 24 months + dietary assessment for Ca intake using a 3 day diet record	• High Ca intake led to lower weight gain and body fat after 2 years of intervention, regardless of the exercise group allocation

Table III. Effectiveness of RCTs to control Metabolic Syndrome

Ca = Calcium; DHA = Decosa Hexanoic Acid; EPA = Eicosa Pentanoic Acid; hs-CRP = High sensitive C Reactive Protein; MeD = Mediterranean Diet; MeDE = Mediterranean Diet + Exercise; MetS = Metabolic Syndrome

Considering effectiveness of specific food items in MetS reduction, consumption of boiled artichoke meal had no beneficial effect in patients (n=19) with MetS in a RCT which was undertaken to ascertain if artichoke could be beneficial in lowering the post – prandial glucose levels and insulin levels in MetS patients [87]. However, Lerman et al. [88] demonstrated benefits from a Mediterranean-style, low-glycemic-load diet (n=12) and phytochemical-enhanced diet (n=12) consumed over 12 weeks period coupled with identical aerobic exercise counselling. The phytochemical-enhanced diet comprised of low-glycemic-load diet plus a medical food containing soy protein and plant sterols and a nutraceutical containing hops rho iso-alpha acids and acacia proanthocyanidins. Improvement in the levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), cholesterol/HDL-C, triglyceride/HDL-C, apolipoprotein B (apo B), apo B/apo A-1, homocysteine, total LDL particle number, and large HDL particle number were observed in the phytochemical enhanced diet group compared to only Med diet group (p<0.05). Nuts, as a MeD component, have shown additional benefits regarding improvement of the syndrome, if incorporated along with lifestyle counselling. In a RCT [89] among 283 MetS screened patients, 30 g/d flaxseed or 30 g/d walnuts were given with lifestyle counselling, while the third group received only counselling. Post 12 weeks, prevalence of the syndrome decreased significantly in all 3 groups. However, the severity was most significantly reduced in the walnuts group compared to only lifestyle counselling group (p=0.045). Similar reduction in MetS has also been observed with food containing phytosterols and soy proteins [76]. Therefore, specific foods such as nuts or phytochemicals might have a potential in prevention and management of the syndrome, however, more work is clearly warranted in this area to bring out their effectiveness.

Which is the best dietary composition to combat MetS?

Though diet and lifestyle modification seem to be the first line of treatment for the syndrome, the uncertainty with the exact diet composition for reduction of the syndrome still remains elusive [90]. Two diets viz. diet relatively rich in carbohydrate (65% of energy as carbohydrate, 13% as protein, and 22% as fat: 17% as unsaturated fat) or a diet that was low in carbohydrate and high in protein and in monounsaturated fat (48% of energy as carbohydrate, 19% as protein, and 33% as fat: 24% as unsaturated fat), differing in their composition were tested on 100 obese patients with MetS. At the end of 5 months, though the syndrome components decreased in both diet groups, a greater significant decrease in hypertension (p<0.05) prevalence and hypertriacylglycerolemia (p< .001) were seen with the low carbohydrate (CHO) diet group [90]. Alleviation of the factors determining the syndrome was ascertained via a low calorie diet with or without exercise, in 323 overweight Japanese women (24-67 years; BMI: 25-40 kg/m^2) in a 3 months program. CART (Classification and regression tree) analysis revealed that a weight reduction of 8.1% in baseline body weight resulted in improvement of at least 1 MetS component was observed among women ≤ 41.5 years; ≥ 13.0% weight loss led to improvement in abdominal obesity; improvement in blood pressure; ≥ 13.2% weight loss led to improvement in hyperglycemia. Thus, a modest weight loss of 8-13% was nearly effective in ameliorating individual components of MetS in overweight Japanese women [91].

Dietary modification to counter the syndrome is also an important strategy to reduce cardiovascular risk. Four diets were randomly assigned to 337 patients: two high fat diets, one rich in saturated fat (HSFA) and the other rich in monounsaturated fat (HMUFA), and two low fat diets, one high in complex carbohydrates (LFHCC) supplemented with 1.24 g/day of long-chain n-3 polyunsaturated fatty acids (LFHCC n-3) and the other LFHCC diet with placebo (LFHCC). Decrement in the prevalence of MetS (p<0.028), lowering of waist circumference, blood pressure and hypertriglyceridemia (p<0.05) was observed with the LFHCC n-3 diet in contrast to HSFA, HMUFA and LFHCC groups [92]. Meal replacement can also be an effective technique in reduction of MetS risk factors even over a short period of time. Ninety overweight or obese subjects (45 years; BMI 31.5 ± 2.3 kg/m^2) were either randomized to a fat restricted low calorie diet group (LCD-G) (n=30) which received 2 dietary counselling

sessions and instructions on physical activity or in the meal replacement diet group (MRD-G) (n=60) that received the same lifestyle education and replaced 2 of their meals with low calories high protein soy drink. Subjects in the MRD-G lost significantly more weight (p<0.01), had higher reduction in WC (p<0.01), triglycerides (p<0.01), syndrome prevalence (p<0.05), leptin and insulin levels (p<0.01) in comparison to LCD-G [93]. Often, it becomes difficult to attribute exactly whether weight loss or behaviour change or both are responsible for successful reduction of the syndrome [94]. This pertinent aspect led to investigation in men and post menopausal women with elevated LDL and lowered HDL, to ascertain the effects of low fat diet and exercise – alone and in combination, on MetS. Maximum change in MetS was observed with low fat diet in men (p=0.04) and women (p=0.045) in comparison to controls. Yet, after adjustment for body fat change, there wasn't any effect of low fat diet and exercise on the syndrome. As a result, it was the body fat that had a significant association with MetS in both men (p<0.0001) and women (p=0.004), and emerges as the crucial component to be targeted [94]. Hence, through the evidence cited, it appears that low calorie diets have the potency to cause a resultant decrease in various components of MetS.

Lifestyle modification

The term 'Lifestyle' implies the way of living. It encompasses the existence of individuals, families and societies with their corresponding behaviour in different settings such as physical, social, psychological and economic [95]. With industrialization, emergence of lifestyle diseases is on the rise, owing to longer life span and faulty lifestyle. The resultant non-communicable and chronic diseases impose burden on the health services of a country especially the developing nations, leading to longer years of disability and death, eventually leading to poor productivity, and thus, hampering the growth of a nation [95]. Hence, interventions to promote healthy lifestyle to curb the development of MetS are the need of the hour (Table IV). Regular physical activity along with proper diet i.e. rich in fibre, low calorie or energy restricted, has shown beneficial effects in reduction of MetS [96], increase in the intake of fruits and vegetables [96,97], decrease in BMI, WC, triglycerides, LDL, insulin resistance [98-100] and inflammatory markers such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) [99].

Most lifestyle intervention programs are based on weight reduction that has proved successful, demonstrating significant improvements in all components of the syndrome [101-103].

Ref.	Duration	Sample	Intervention	Finding(s)
[96]	10 weeks	N=50 overweight adults (n=22 general educational group; n=28 high fibre nutrition group)	Lifestyle intervention focusing on physical activity and high fibre intake via dietary counselling and supervised exercise	• Higher intake of fruits and vegetables, higher plasma β-carotene levels, greater reductions in body fat, waist circumference, obesity class III, obesity class II and 24% reduction of MetS was seen in the group 2 as compared to group 1
[97]	6 month intervention	N=816 male blue and white collar workers	Intervention consisted of individual counselling using motivational interviewing techniques, and was delivered by an occupational physician or occupational nurse	• Statistically significant improvement in the snack (b-1.9, 95%CI = -3.7; -0.02) and fruit intake (b 1.7, 95%CI = 0.6; 2.9) at 6 months • Sustained snack and fruit intake improvement at 12 months • Beneficial impact on smoking (OR: 0.3) at 6 months • No significant impact on leisure time physical activity

> follows

Ref.	Duration	Sample	Intervention	Finding(s)
[98]	6 months	N = 60 (mean age 40.0 ± 8.5 years) non-alcoholic fatty liver disease (NAFLD) patients	Regular aerobic exercise for 30 min/d, for at least 5d/week + Moderate Energy restricted diet containing 60% carbohydrate, 20% fat, 20% protein and 200mg cholesterol (NCEP Step I diet, (25 kcal/kg ideal body weight) was advised to patients with high BMI	• Significant decrement in BMI, WC and Alanine amino Transferase (ALT) was observed post 6 months (p<0.01) in 45 exercise compliant patients • No significant changes in BMI, WC and ALT were seen in 15 non-exercise compliant patients
[99]	3 week intervention + 6 month follow-up	N= 14 (10 men, 4 women, mean age 62.9 ± 6.9 years) adults with MetS	Balanced diet corresponding to 500 Kcal deficit vs. their daily energy expenditure (DEE) and they exercised 2 to 3 hours per day	• Significant improvement in triglycerides, total, LDL and HDL cholesterol, insulin, leptin and adiponectin levels, CRP and pro-inflammatory interleukines IL1, IL6 and TNF α were observed at 3 weeks • No changes in cytokines were observed • Changes were sustained at 6 months
[100]	1 year	N=130 (37% African American) severely obese (class II or III) adults without diabetes	Group1: diet + physical activity 12 months; group2: diet but physical activity only from 6 months onwards)	• Weight loss in group 1 was more significant as compared to group 2 at 6 months (p=0.02) • Similar weight loss in both groups at 12 months (p=0.25) • Reductions in Waist circumference, visceral abdominal fat, hepatic fat content, blood pressure, and insulin resistance in both groups
[135]	Ongoing	N=4,600 (5-40 years)	Intensive (3-monthly) lifestyle modification advice is superior to a less-intensive (12 monthly; control group) lifestyle modification advice	• Ongoing trail: follow up post 5 years of intervention • Aims to reduce the prevalence of DM, Pre-Diabetes and MetS
[136]	Short-term = 12 weeks and long-term = 24 weeks	N=66 obese adolescents (41 girls and 25 boys; BMI: 35.62 ± 4.18 kg/m²)	Multidisciplinary lifestyle therapy composed of medical, dietary, exercise and psychological programs	• Long term therapy resulted in decreased depression and binge eating symptoms, body image dissatisfaction, and improved QOL in girls (p<0.05) • Reduced anxiety trait/state, symptoms of binge eating and improvement in QOL was observed in boys (p<0.05)
[137]	12 week	N=49 (aged 25-80 years) MED (n=19); PED (n=25)	MED-Mediterranean-style, low glycemic load diet group; Phytochemical enriched diet (PED)-Mediterranean diet + phytochemicals	• Weight loss was achieved in both groups • More significant reductions in the cholesterol levels, triglycerides, cholesterol/HDL and TG/HDL ratio was observed in PED group (p<0.05) compared to MED • Increased HDL(p < 0.05), decreased TG/HDL(p < 0.01),and resolution of more number of patients (43%) from MetS was seen only in the PED group
[138]	12 weeks	N= 59(n=20 WL; n=20 WL+EX; n=19 control)	dietary weight loss (WL, n=20); dietary weight loss and moderate-intensity aerobic exercise (WL+EX, n=20); no treatment (n=19)	• Decrement in body weight (P < 0.001), Resting SNS activity (p<0.01), muscle sympathetic nerve activity (p<0.01) was observed in both WL and WL+EX group • Increment in fitness levels were seen only in WL+EX group (P< 0.001)

Table IV. Role of Lifestyle interventions (RCTs) in combating MetS and its components

ALT = Alanine Amino Transferase; BMI = Body Mass Index; CRP = C Reactive Protein; DEE = Daily Energy Expenditure; DM = Diabetes Mellitus; EX = Exercise; HDL = High Density Lipoprotein; IL-1 = Interleukin 1; IL-2 = Interleukin 2; LDL = Low Density Lipoprotein; MetS = Metabolic Syndrome; NAFLD = Non-Alcoholic Fatty Liver Disease; PED = Phytochemical Enriched Diet; QOL = Quality of Life; SNS = Sympathetic Nervous System; TG = Triglycerides;TNFα = Tumor Necrosis Factor α; WC = Waist Circumference; WL = Weight Loss

A therapeutic lifestyle program (TLM) is the most sought after way of tackling the syndrome. A hospital based intervention consisting of a low calorie diet and regular aerobic physical activity was conducted for 8 weeks in women (n=44) with MetS. Significant decrease in all MetS components except HDL-C, along with complete amelioration of the syndrome in 25% of women was observed [104]. Impact of TLM was also assessed among the rural women (n=32) with MetS who were randomized to a 4 week intervention consisting of health screening, education, exercise, diet and counselling, while a basic education booklet on MetS was provided to the control group. Significant reduction in the body weight, waist circumference, triglyceride levels, and positive behaviour change was noticed in the intervention group compared to the control group (p<0.01). A positive time effect was noticed with the intervention group which resulted in decrement in the systolic blood pressure, fasting glucose, and LDL levels, and increment in the HDL levels, thus, substantiating the role of a TLM intervention in MetS improvement [105]. Another lifestyle intervention encompassing healthy diet evaluating the metabolic and vascular changes that occur with the syndrome was carried out. Seventy five adults with MetS (30-55 years) were randomized to a 10,000-steps-a-day exercise program + healthy, no-sugar diet; a 3-times-a-week fitness (>75% peak VO2) program + healthy, no-sugar diet; and a 1-hour-walking-a-day program + a tailored low-fat diet for 12 weeks. Significant increase in Flow Mediated Vasodilation and decrease in arterial pressure was maximum in the high intensity, no sugar group (p=0.036), wherein, arterial pressure decrease (p=0.0001) and weight loss (p=0.0001) was maintained post 1 year [106]. Similarly, a pilot study comprising 150 minutes of regular exercise, 200-300 kcal reduced daily diet for weight reduction, individual psycho-behavioural counselling based on Trans theoretical model and telephone coaching for behavioural modification, on 43 Korean adults with Type2 DM and MetS proved to be beneficial (p<0.05) leading to better glycemic control, lessened CVD risk, and depression [107]. So, weight reduction seems to be a good strategy to target as a component of the syndrome that has the potential resulting in improvement of the other components of the syndrome.

Interventions at the genetic level

Role of genetics in the pathobiology of the syndrome, though small, is extremely significant [108]. Since MetS is an outcome of both environmental as well as genetic factors, a dietary intervention (12 weeks) was undertaken in women (n=24) with the syndrome, to observe any change in the expression of LDL receptor and 3-hydroxy-3-methylglutarylcoenzymeA (HMG-CoA) reductase genes. Significant decreases in WC (p<0.001), plasma triglycerides (p<0.05), systolic blood pressure (p<0.05), LDL-C (p<0.01), plasma insulin (p<0.001), plasma TNF α (p<0.01), and homeostatic model assessment score for insulin resistance (HOMA-IR) (p<0.001) were observed post-intervention. Though no change in the LDL cholesterol gene expression was detected, reduction in HMG-CoA reductase gene expression (p<0.001) was observed [76]. This is an important finding as HMG-CoA reductase is the key regulatory gene in cholesterol synthesis that can ultimately lead to lowered very low density lipoprotein (VLDL) levels and correspondingly decrease LDL cholesterol. Modulation in the genetic expression of other genes have also been observed with a dietary intervention focusing on MeD in patients with MetS (n=20) and high CVD risk (n=49). It resulted in changes in the genetic expression of cyclooxygenases 1 and 2, monocyte chemotactic protein 1, low-density lipoprotein (LDL) receptor-related gene, and pro-inflammatory genes. So, alongside environmental factors, an understanding of the genetic factors is also essential to customize treatment strategies [109].

Inflammation: an important component of intervention strategy

Several contributory factors such as abdominal obesity, dyslipidemia, impaired glucose tolerance, high blood pressure and prothrombotic state lead to the development of MetS [110]. Studies relating low-grade inflammation to MetS have been reported, with various biomarkers like increased C-reactive protein (CRP), increased IL-6, increased TNF, decreased IL-10, decreased adiponectin, increased

leptin, increased Serum Amyloid A (SAA), increased resistin and increased Plasminogen Activator Inhibitor-1(PAI-1) being responsible for it [111]. Chronic low-grade inflammation is associated with insulin resistance. One of the main components of the inflammatory process is cytokines, particularly, IL-1, TNF and IL-6, of which IL-6 is the central mediator of inflammatory response. Its relationship with insulin, mediated through adiposity, links it to MetS. Another proinflammatory cytokine viz. TNF, secreted to a large extent by adipocytes, is an important regulator of insulin sensitivity, which decreases with weight loss. Besides these, other markers such as adiponectins are also associated with MetS [111]. Interventions to target MetS have shown an impact on its markers such as circulating adiponectin. Forty four obese adolescent obese girls (13-15 years), who were randomized to a lifestyle plus exercise intervention group (LIFE+EX, n = 22) or control (CON, n = 22) for 12 weeks, resulted in improvements in body composition, waist circumference, waist-to-hip ratio, and significant reductions in blood pressure, triglycerides, LDL levels, glucose, insulin, HOMA-IR, CRP, and leptin compared to the controls. However, no change was observed in the circulating adiponectin levels [112]. Metabolic alterations associated with MetS particularly, decrement in the levels of metabolic variables and CRP values were gauged for their affiliation with diet/exercise variation. In a prospective randomized control trial of 169 cases and 166 controls [113], exercise levels were inversely associated with CRP (p<0.001), as fibre intake was with fasting glucose (p<0.001), independent of weight reduction. Changes in the C-reactive protein with either a low fat diet or physical activity or both was demonstrated among men (n=149) and post menopausal women (n=125) in a 1 year RCT. Significant changes in CRP in both diet + physical activity group was more than physical activity group only (p=0.02). Any diet treatment with or without physical activity also had greater CRP change than the control (p=0.001), thus, demonstrating the efficacy of a low fat diet for reduction of the syndrome [94].

A recent review proposed the role of interleukin-18 (IL-18) in the pathogenesis of diabetes and MetS, as a predictor of cardio-vascular events and mortality. IL-18 results in induction of inflammatory reactions being present in the adipose tissue, atherosclerotic plaque and in the muscle tissue, therefore, can act as a marker of chronic low-grade inflammation [114]. The association of MetS with beta 3-adrenergic receptor (ADRB3) Trp64Arg polymorphism was examined in 36 male employees with MetS (average age, 49 ± 6 years old) undergoing a three month intervention. There was 53.8% improvement in the MetS post intervention in participants with ADRB3 Trp64Arg polymorphism, supporting its role in influencing the syndrome coupled with an exercise-based intervention program [115]. The relationship of inflammatory markers and their possible role in the pathogenesis of MetS have a unique prospect in combating the syndrome as various repercussions associated with the syndrome are correlated with them. Development of cost-effective strategies for evaluation of these markers needs to be done so that they can be used for prevention as well as treatment of the syndrome.

Early intervention: need of the hour

Early interventions have a better potential of targeting the syndrome than doing it at a later stage, where much improvement cannot occur. A multidisciplinary school based intervention can be a promising strategy [116]. This was carried out in overweight and obese adolescents (n=37 intervention group; n=39 control; age: 17.3±1.3 years; BMI: 29.5±3.7 kg/m^2) who were encouraged to adopt a healthy lifestyle, coupled with consultations from dieticians and physiotherapists, and a free membership to a nearby fitness centre. After 6 months of intervention significant weight loss (p<0.001), change in BMI (p<0.001), decrement in WC (p=0.011) and fasting glucose (p=0.005) was observed compared to the control group, thus, guaranteeing the usefulness of a multi disciplinary intervention program [117]. Rarity of lifestyle interventions in obese children leads to the possibility of development of MetS in future. Obesity and overweight in children can thus, have serious ramifications if not controlled sooner enough projecting to high risk for development of MetS and subsequent CVD in adulthood [118,119]. A lifestyle intervention with obese children (n=288 intervention group; n=186 control group) led to a

significant decrease in BMI, WC, oral glucose tolerance test (OGTT) values, blood pressure and MetS prevalence in the intervention group as compared to controls [120]. A rigorous lifestyle intervention, in which a high-fibre, low-fat diet in a 2-week residential program where food was provided ad libitum, and daily aerobic exercise was performed, was carried out in 16 overweight and obese subjects. Post 2 weeks of intervention, significant decrement in insulin level (p<0.01), HOMA insulin level (p<0.05), body weight (p<0.01), total cholesterol (p<0.01), LDL (p<0.01), triglycerides (p<0.01), LDL/HDL ratio (p<0.01), systolic blood pressure (p<0.001) and diastolic blood pressure (p=0.01); however, no change was observed in HDL-C levels. Of the 7 patients who were diagnosed with MetS, the syndrome reversed in all of them [121].

Evidence generation from intervention trials: development of public policies

For development and improvement of the public policies, evidence generated through intervention trials holds the key. However, sustainability is an important issue with respect to most interventional studies which falter in the long run because of poor compliance and low cohesion rates [122-125]. Restrictions in diet only serve the purpose as long as they aren't overtly limiting; as chances of rebound and the intensification of the appetite with reference to too many restricted foods isn't inevitable [126]. It holds the key to behaviour change in confronting MetS. Though, intensive, individualized lifestyle intervention programs are the most appropriate step for increasing sustainability; cost and time are limited [127]. A 16 week group based intervention, economical in terms of cost and time was formulated for 153 obese/overweight individuals focusing on dietary and physical activity information, behavioural self management tools, food label reading, supermarket tour and cooking, exercise sessions and peer group support. Usefulness of various components of the intervention was reported by participants in the intervention group compared to controls. Such programs bring out the need of active training in lifestyle modification rather than passive provision of guidelines in the form of a booklet. Weight loss and weight maintenance are two important concepts that go hand in hand. Weight loss alone can't be the criteria for tackling MetS, because if the lost weight is not sustained chances of rebounding is high [128]. Weight loss maintenance in an intervention (n=14 males; 4 females) resulted stable energy balance affected sympathetic nervous system activity leading to decrement in nor epinephrine spill over rate (p=0.004), muscle sympathetic nerve activity (p<0.001), and plasma rennin activity (p=0.007), and increment in baroreflex sensitivity (p=0.005). Compliance and adherence are two substantial perspectives that need to be addressed whenever lifestyle intervention programs are implemented for syndrome's reduction. Though there have been studies regarding the implementation of these programs, sustainability is the issue that has been neglected often. Therefore, approaches to increase sustainability are required for combating the syndrome effectively [129]. With substantial health consequences, it becomes all the more important that MetS needs to be targeted, and physical activity along with diet improvement is one such measure that has the ability to attenuate the syndrome if performed methodically [96,128,130].

Conclusion

With westernization of the worldwide dietary pattern, MetS is reaching epidemic proportions, wherein, diet and lifestyle interventions are regarded as the first line of defence for combating it [131]. The consequences of globalization and industrialization are the emergence of lifestyle related NCDs contributed by unhealthy dietary patterns, lack of physical activity and smoking as well as alcohol abuse.

Future directions for research

Future studies should be undertaken focusing on carrying out interventions (diet and lifestyle) among young adults in whom the prevalence of the syndrome might be low but have a great potential of developing it in future if no action is taken early. Development of appropriate strategies to increase the sustainability of these interventions must be accomplished to combat the syndrome. The diagnosis and severity of the syndrome should be based on uniform diagnostic criteria considering population, country and ethnicity. Since, there are a multitude of risk factors that eventually lead to MetS, longitudinal studies should be conducted to understand the interaction among these factors. Future studies should concentrate on determining a suitable dietary composition that could be considered as a template for alleviation of the syndrome. Special attention needs to be drawn on genetics as well as inflammatory markers such as IL, CRP, adrenagic receptors etc, which can be used in the development of cost-effective strategies for prevention and treatment of MetS.

With only a handful of people following the healthy diet and lifestyle, majority still fall in the bracket of those with compromised diet and lifestyle, burdening the health services [95]. Socio economic changes and eventually globalization has led to transformation in the society. This has led to alterations in the dietary habits eventually resulting in nutrition transition [132]. A first line intervention targeting MetS involves dietary and lifestyle modification with regular physical activity over a period of time. However, improvement in MetS parameters can only be maintained when these modifications can be sustained. This requires multiple follow up sessions post-intervention rather than one counselling ses-

The review in brief	
Clinical question	Dietary and lifestyle modification has been underlined as the first treatment to combat Metabolic Syndrome by AHA. The present review analyzes the role of dietary and lifestyle modification as an effective strategy to reduce the syndrome.
Type of review	Narrative
Search of the literature	Medline, PubMed (National Library of Medicine, Bethesda, MD, USA), Cochrane Library, Science Direct and Google Scholar search using the following keywords: Metabolic Syndrome, diet, lifestyle, Mediterranean diet, intervention, insulin resistance, obesity, non- communicable diseases, hypertension, HDL, triglycerides, inflammation, genetics, CRP
Conclusions	The present review concludes that: • MetS is a complex entity that is a result of multitude of factors. • Dietary and lifestyle modification is the first line of treatment for prevention of the syndrome. • Mediterranean and low calorie diets have the potency to cause a resultant decrease in various components of MetS. • Regular physical activity along with diet improvement has the ability to attenuate the syndrome if performed methodically. • Weight reduction resulting from dietary and lifestyle modification has proven beneficial in combating the syndrome. • Alongside environmental factors, an understanding of the genetic factors and inflammatory markers is also essential to customize treatment strategies. • Early interventions have a better potential of targeting the syndrome than doing it at a later stage, where much improvement cannot occur.
Limitations	Though various studies involving dietary and lifestyle modification have shown benefits by resulting in the improvement of various components of the syndrome, the emphasis needs to be laid on carrying out research that ultimately looks at the sustainability and compliance with such interventions, in order to show their efficacy on a long-term basis.

sion involving the use of several behavioural techniques to improve compliance [133]. For development and improvement of the public policies, evidence generated through intervention trials holds the key. Therefore, dietary and lifestyle modification in continuum is required to overcome MetS holistically.

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