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Review Article

Combating Metabolic Syndrome through Non-Pharmacological Strategies: A Literature Review

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ABSTRACT

Metabolic syndrome (MetS) represents a constellation of interlinked metabolic abnormalities, encompassing hypertension (HTN), insulin resistance diabetes, obesity, and atherogenic dyslipidemia. It is observed that people suffering from these symptoms of metabolic syndrome are twice as likely to develop cardiovascular diseases (CVDS) and five times more likely to develop Type 2 Diabetes Mellitus (T2DM) during their lifetime. The alarming increase in the incidence of MetS, in population worldwide, has made it an epidemic. In today's world people are more susceptible to MetS due to their sedentary lifestyle, bad eating habits, and various forms of stress. Knowing the socioeconomic burden of disease of MetS on global health throughout the years has brought attention towards its management and therapeutic approach and rightly so, this has also created the need for new, innovative, and non-traditional methods of managing MetS, as the current available treatments of MetS have limited efficacy. In this review, we highlight the prevalence, definition and also summarize the latest non-traditional therapies of MetS worldwide.

INTRODUCTION

Metabolic syndrome, also known as syndrome X or Reaven's syndrome, is a cluster of diseases encompassing cardiovascular diseases (CVDs), Type 2 Diabetes Mellitus (T2DM), and stroke [1, 2]. The risk factors of MetS include abdominal obesity, atherogenic dyslipidemia, hypertension, and insulin resistance [2]. If more than 3 criteria are present then it is called metabolic syndrome [3]. Typical traits of MetS are hyperglycemia, atherogenic dyslipidemia, and hypertension and people with these traits are twice at the risk of developing CVDs and 5 times more for T2DM[4].

Obesity and insulin resistance are believed to be at the core of most cases of metabolic syndrome [4]. The standard of care for managing MetS continues to be pharmaceutical intervention along with dietary and exercise modifications to promote weight loss[5].

Prevalence

In the past, MetS was a disease in Western countries,

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recent research has shown that over the past decade prevalence of MetS has increased exponentially in urban populations of developing countries [6] and future prediction indicates that it will continue to grow in rural populations too. It is estimated that the global prevalence of MetS is over a billion people (12.5% to 31.4%) with a prevalence of 2.8 % in children and 4.8% in adolescence. It is interestingly, closely associated with the number of incidences of T2DM, obesity, and CVDs [7].

Pathophysiology

It is widely known that in the 1980s, Reaven put forward the idea of MetS, under the term Syndrome X, where he put insulin resistance at the core of the problem leading to CVDs and T2DM [8]. Ever since then, there has been significant research done to understand the mechanism of MetS and the pathophysiology behind it, yet there are still many different points of contention regarding its pathophysiology and definition. Numerous intricate mechanisms make up the pathophysiology of the MetS, many of which are still not fully understood [9]. The question of whether the various MetS components constitute separate pathologies on their own or are part of a single, more general pathogenic process is still up for debate. Some lifestyle and environmental factors, including overeating and lack of physical activity, have been recognized as key contributors to the development of MetS in addition to genetic and epigenetic factors [10]. Since visceral adiposity has been found to be a significant trigger that activates most of the MetS pathways [11], high caloric intake can be attributed to a causal role [6]. Among the suggested pathways, neurohormonal activation, chronic inflammation, and insulin resistance appear to be key players in the development of MetS and associated symptoms [6].

Criteria

Moreover, there are also no set criteria for accessing MetS universally. There are three widely known definitions given by the World Health Organization (WHO), National Cholesterol Education Program Adult Treatment Panel III (NCEPATP III) AND International Diabetes Federation (IDF) as shown in the Table 1A and 1B below.

Table 1A: Dissimilarities in the definition of Metabolic Syndrome as defined by WHO, NCEPATP III and IDF

World Health Organization (WHO)	National Cholesterol Education Program Adult Treatment Panel III (NCEPATP III)	International Diabetes Federation (IDF)
METS patients will have at least two of the following findings: Central obesity, or dyslipidemia, or raised Blood pressure or taking meds for previously diagnosed hypertension as well as hyperinsulinemia, or hyperglycemia.	METS patients will have three or more of the following five conditions: High waist circumference, high Blood pressure, Increased cholesterol, low HDL levels High fasting Blood sugar levels.	People with central obesity & any 2 of the following factors constitute METS: Raised triglycerides, reduced HDL cholesterol, Elevated Blood pressure and Elevated fasting plasma glucose or previously diagnosed T2DM.
Waist Circumference greater than 94cm.	Waist circumference greater than 102 cm for men and 88 cm for women.	Waist circumference >90 cm for South & East Asian men &>80 cm for South & East Asian women
Triglycerides levels greater than 140/90 mmHg or HDL cholesterol less than 40 mg/dl.	Fasting Triglyceride levels greater than 150 mg/dl.	Triglycerides>150 mg/dl reduced HDL cholesterol less than 40 mg/dl in men & 50 mg/dl in women.
Blood pressure greater than 140/90 mmHg	Blood pressure greater than 130/85 mmHg.	Blood pressure greater than 130/85 mmHg.
Fasting glucose more than 110 mg/dl.	Fasting glucose more than 100 mg/dl.	Fasting glucose more than 100 mg/dl or previously diagnosed with Type II Diabetes Mellitus.

Table 1B: Similarities between definition of metabolic syndrome as defined by WHO, NCEPATP III and IDF

Organizations	Similarities in Definition
World Health Organization (WHO)	**Common Risk Factors:** WHO, NCEPATP III and IDF consider the following risk factors to be the main cause of Metabolic Syndrome which include: 1. Elevated blood pressure and 2. Fasting blood glucose levels, 3. Abdominal obesity 4. Abnormal lipid profiles. **Cardiovascular Risks:** All three of these organizations highlight the necessity of identifying individuals at risk for Metabolic Syndrome as a group of risk factors for cardiovascular diseases.
National Cholesterol Education Program Adult Treatment Panel III (NCEPATP III)	
International Diabetes Federation (IDF)	

Interestingly, Eva and colleagues wrote that because of no universally accepted criteria for MetS, there has been a significant focus on finding the right diagnosis rather than assessing existing risk factors of MetS in individuals [12]. Unfortunately, this also takes away from creating criteria and setting a gold standard treatment plan for better management of MetS. However, Saklayen notes in his article that the region-wise differences in definition and criteria of MetS are minor and can be overlooked due to the more grave issue of socioeconomic disease burden that is causing the entire world population and healthcare system to succumb under [13]. It is safe to say that the overall cost of the illness, including medical expenses and lost potential economic output, is in the trillions of dollars. The current trend cannot continue until a miraculous treatment is discovered, or unless significant efforts are made on a global, governmental, and cultural level to alter the way of life that is encouraging it [13].

Management of Metabolic Syndrome according to Types of Diet

Following are different management strategies of Metabolic Syndrome according to diet.

Mediterranean Diet

Over the years, there has been a new approach in preventing MetS and that is with the ancient Mediterranean diet. The Mediterranean diet consists of vegetables, legumes, fruits, nuts, cereals, fish and seafood, monounsaturated fatty acids, dairy products, and

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moderate alcohol consumption. People consuming this diet do not require salt intake as they supplement it with herbs and spices which not only help in decreasing blood pressure after consumption but also add flavor to the food. The main source of fat in this diet is extra virgin olive oil (EVOO) which has proven to be beneficial in preventing T2DM [14]. In a recent study, 80 patients with new onset diabetes when treated with MedDiet and EVOO showed improved glucose metabolism and a decrease in body weight [15, 16]. The main component of this diet usually consists of polyphenols present in olive oils, red wine, and citrus fruits [17]. This chemical can inhibit the ACE pathway and therefore regulate blood pressure [18]. However, there are a few limitations with the Mediterranean diet, firstly there is a chance of weight gain from eating more than the recommended amount of fat, secondly, there could be chances of anemia due to not consuming an adequate amount of meat, and calcium deficiency due to consumption of fewer dairy products. Also, the Mediterranean diet is overall costly for low socioeconomic populations. Alcohol consumption is restricted in some cultures around the world, this causes a discrepancy in the data provided as different religions prohibit alcohol consumption.

The Vegan Diet

The vegan diet is plant-based specifically excluding all animal-origin foods, unlike vegetarian diets where dairy products, eggs, and honey can be consumed. The vegan diet consists of cereals, vegetables, legumes, seeds, nuts, and vegetable oils. This diet is generally high in alpha-linoleic acid. Alpha-linoleic acid helps in lowering blood pressure, and cholesterol levels and reverses atherosclerosis. A collection of scientific data shows that a vegan diet can promote or restore good health [19]. People adopt this diet due to ethical, health, and environmental reasons, however, in the current trends, the vegan lifestyle should be recommended by healthcare providers due to its positive effects on T2DM, CVDs, and MetS [20]. However, this diet has a few limitations. If it is not consumed in a well-balanced portion, it can cause serious deficiencies in proteins, omega 3 fatty acids, iron, vitamin D, calcium, zinc, and vitamin B12 due to which people are easily susceptible to megaloblastic anemia, kwashiorkor, and marasmus [21]. There is clear evidence that such diets may cause lower bone mineral density and therefore increase the risk of multi-site fractures in consumers [22]. Although research is needed on physiological factors, it is also believed that endocrine profile, BMI, and microbiome may also play a certain role in causing these fractures. Therefore, the use of oral food supplementation along with a vegan diet is required to overcome the above-mentioned nutritional deficiencies [23]. Additionally, athletes following vegan diets may have trouble achieving protein needs for muscle retention, recovery, and increased appetite needs as compared to non-athletic people [24]. Therefore, athletes taking vegan diets once again require additional oral food supplementation. Lastly, another drawback of following a vegan lifestyle is the high cost of sourcing plant based food, in areas where plant-based diets are not commonly found or grown.

Intermittent fasting vs. Calorie restriction diet

Intermittent fasting(IF) also known as alternate-day fasting, other full-day fasting patterns, and time-restricted eating [25] can be defined as consuming 500-700 kcal for 2-4 days/week [26] whereas calorie restriction diet (CR) follows restriction of total calorie intake in a day. Recent studies show that the risk of developing age-related diseases can be decreased by intermittent fasting due to its effect on lowering blood sugar, insulin, fat, and circulating glucose levels [27]. In patients with obesity and type 2 diabetes, clinical trials revealed that 2-day IF significantly reduced body fat mass, improved insulin resistance [28], and improved glycated hemoglobin and glycemic control [28]. Some common pathways that IF intervenes in are autophagy, mitochondrial function, and adaptive cellular response [29]. It also appears to regulate the circadian rhythm of hormones, especially insulin among others [30]. The rising popularity of IF is attributed to its compatibility with human eating patterns as opposed to a continuous restricted diet where several trials have suggested that people had trouble following CR over an indefinite period of time [31]. However, there is still debate concerning IF's long-term negative consequences in people, including hypoglycemia, digestive system harm, and impaired bone metabolism [32]. The lack of data supporting the negative consequences of intermittent fasting regimens is mostly due to the short time frames used to evaluate them (weeks to months). Hypoglycemia, vertigo, and weakness are a few of the often reported negative effects [30].

Coffee and Tea

Coffee and tea are the most commonly consumed beverages in the world. They have become an important part of an average person's diet. It has been discovered that the use of coffee and tea can help in preventing and also combating obesity [33, 34]. Moreover, they can reduce appetite, decrease food consumption, and simultaneously, food absorption in the GIT, as well as increase fat metabolism [35]. It is believed that they exhibit these effects because of the main primary component called caffeine (1,3,7 trimethyl-xanthine) [35]. Tea: The active ingredient in tea is polyphenols [35]. Polyphenols exhibit anti-inflammatory effects on the Gastro-intestinal tract. Moreover, the molecules of tea in the right ratio can also

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counteract anxiety and stress [36]. According to a study carried out on animals and humans, it was reported that tea reduces the prevalence of metabolic syndrome, cardiovascular diseases, and diabetes [37]. Another study stated that green tea polyphenols can cause reduced glucose blood levels by acting on glucose production in the liver [38]. Most studies support the fact that tea has a positive impact on patients with MetS. However, some studies demonstrate no effect on the concentration of glucose, fatty acids, and triacylglycerols [39, 40]. Coffee: Other than caffeine, the major component of coffee is chlorogenic acid [41]. Chlorogenic acid has antioxidative and anti-inflammatory effects on body cells. These effects show to have preventative and therapeutic influence against diabetes and CVDs [41]. Coffee consumption can also be recommended not only to healthy and young people but also to people with high blood pressure, cholesterol, and blood glucose as well as people with MetS [42]. Many other studies have shown a correlation between the habit of drinking coffee and reduced mortality due to CVDs [43]. However, coffee if consumed in large amounts can cause insomnia, anxiety, and loss of calcium which can further lead to osteoporosis [44]. Coffee can also damage sperm and prolong pregnancy [45].

Curcumin

Curcumin is a yellow pigment found in turmeric. It is a type of polyphenol. It contains (1) anti-inflammatory, (2) anti diabetic, (3) antioxidative, (4) anti atherosclerotic, and (5) hepatoprotective properties. According to a study, it was found that curcumin decreases serum LDL, total cholesterol, and triglyceride levels [46]. It helps to reduce fat production by reducing the expression of PPAR and CCAAT/enhancer binding protein alpha as well as lowering cholesterol levels [47]. Moreover, it also increases insulin secretion by upregulating the gene expression of pancreatic glucose transporter (GLUT-2, GLUT3, GLUT-4)[47]. Once GLUT proteins are expressed on the cell membrane, it allows for the uptake of glucose into the cell, effectively decreasing blood sugar levels in the body. One drawback of a curcumin centered diet is that it is found in low concentrations, in turmeric, which decreases its bioavailability, therefore it is given in the form of supplements for therapeutic purposes [47]. Curcumin can be best given with piperine (a component of black pepper). Some studies have shown that the co-administration of these supplements significantly decreased total cholesterol and LDL levels [48]. Another setback of using curcumin supplementation is gastrointestinal disturbances such as nausea and diarrhea [49]. Also in some studies curcumin, in high doses, has shown to exhibit negative side effects on skin cells where proliferation is inhibited [50].

Capsaicin

Capsaicin is the active constituent in chilli. It works by agonistically binding to transient receptor potential vanilloid channel 1 or TRPV1 [51]. This channel is present on many active tissues in the body, mainly heart, liver, kidney, pancreas, and adipocytes. Therefore, it can be suggestive of the fact that TRPV1 can alleviate symptoms of MetS [52]. TRPV1 works by activating sympathetically mediated brown adipose tissue thermogenesis and consequently reduces body fat [53]. In a meta-analysis of 9 studies and 461 patients, it was concluded that capsaicin supplementation showed a positive result in reducing total cholesterol and LDL levels in the blood [53]. Many other smaller studies have shown that capsaicin may decrease lipid levels among patients with MetS, hence it is a good agent to treat dyslipidemia [53]. Another study showed its effective role in body weight control by regulating lipolysis, increasing the feeling of satiety, and stimulating energy expenditure while reducing energy intake [54]. In fact, three major epidemiological studies conducted in different countries found that regular chili consumers had higher cardiovascular morbidity and mortality than non-consumers [55]. However, there is no convincing evidence that dietary capsaicin can normalize blood sugar levels and/or prevent dyslipidemia [55].

Microalgae

Microalgae are unicellular species found typically in freshwater and contain many bioactive components with therapeutic potential, like dietary fiber, carotenoids, vitamins, polyphenols, sterols, and polyunsaturated fatty acids (PUFAs) [56]. Similarly, long chain polyunsaturated fatty acids (LC-PUFAs) like docosahexaenoic acid (DHA) and eicosapentaenoic acid are also present in fishes and fish oils which have shown preventive impact on metabolic unsettling influences related with obesity and decreased risk of CVDs [57]. The decrease in the number of fishery assets due to increased marine contamination requires an alternate source of LC-PUFAs [57]. In this regard, studies have shown that microalgae might prove to be a good alternative to fish oils as microalgae are less delicate to overwhelming water pollution [57]. Several studies done on male Wistar rats fed with high fructose diet (HF) were given supplements of several microalgae to observe its effect on MetS [57]. Tisochrysis Lutea (Tiso) supplements reported that it decreased fat mass, cholesterol, leptinemia, and plasma tumor necrosis factor-alpha levels[57]. This effect of Tisochrysis Lutea (Tiso) is due to its biochemical tolerance and large amounts of DHA that are responsible for decreasing the risk factors of MetS [57]. Supplements of Diacronemalutheri (D.lutheri) decreased the abdominal fat and epididymal adipose tissue weight/body weight ratios as well [57]. It also decreased triglyceridemia and increased the plasma total cholesterol levels and HDL-C

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levels as compared to HF rats [57]. Arthrospira maxima and platensis reduced the fat synthesis in white and brown adipose tissues [57]. Ingestion of spirulina (2-6 g/day) reported the improved insulin sensitivity while supplements of chlorella also appear to have antidiabetic, antihyperlipidemic, antihypertensive, and antioxidative impacts [56].

Probiotics, Prebiotics and Synbiotics

The term probiotics is used to describe bacteria that have a beneficial effect on the human body whereas prebiotics are mostly non digestible fibers [58]. Synbiotics are a combination of prebiotics and probiotics. Recent studies have shown that prebiotics, probiotics, and synbiotics work in three distinct mechanisms, namely modulation of gut microbiota composition, regulation of gut metabolites, and improvement of intestinal barrier function [59]. Rat trials have shown that the use of probiotics has had an overall decreasing effect on blood pressure as they stimulated the expression of ACE enzymes in rats [60]. On the other hand, synbiotics have created a new perspective in obesity prevention because when mixed with probiotics, they showed a more definite reduction in hepatic steatosis and lipid accumulation compared to just probiotics alone [61, 62]. Furthermore, oral supplements containing probiotics and synbiotics showed increased lipid metabolism in obese rats [63]. Additionally, there is countless evidence showing that prebiotic consumption may control the level of gut microbial metabolites such as short chain fatty acids (SCFAs) and bile acids, which may have an impact on the metabolic process [64]. All in all many researchers conclude that gut microbacteria play a role in strengthhening the intestinal integrity [59]. Although the US FDA has provided a list of safe probiotics to use commercially, but they are yet to approve the use of probiotics for medical practice [65]. Moreover, various studies also show the negative effects of probiotic use such as sepsis, pathogenic antibiotic resistance, and hypersensitivity reactions [66].

Coenzyme Q10

Coenzyme Q10 is found inside the mitochondria in the inner mitochondrial membrane where it has an essential role in the electron transport chain transferring electrons from complex 1 to complex 3 [67,68]. Additionally, ubiquinol, the active form of CoQ10, acts as a potent antioxidant in the human body which is why it can successfully stop the initial process of lipid peroxyl radical formation [69]. CoQ10 acts directly on the endothelium in the blood vessel as a vasodilator. This, in turn, decreases blood pressure and helps to alleviate symptoms of hypertension [70, 71]. In another random study where CoQ10 was administered for 12 weeks, it was observed that systolic blood pressure had decreased to normal limits in hypertensive patients [72]. Statins are the most effective and safe medication for the treatment of high cholesterol levels in the body [73], however, one of the side effects of long-term statin use is heart failure due to CoQ10 synthesis inhibition [74]. This problem is countered by the use of CoQ10 supplementation, where one study proved that statins had less side effects compared to their therapeutic effects when used in combination with CoQ10 [75]. Some limitations of CoQ10 supplementation therapy are that despite so many desired effects, still more randomized control trials are required and more data is needed to support its efficacy on MetS [76].

CONCLUSIONS

This literature review explores non-pharmacological strategies for combating metabolic syndrome, focusing on dietary management. A personalized, well-balanced diet can improve metabolic health and reduce the risk of complications. However, dietary management should be part of a holistic approach, including physical activity, stress management, and regular health monitoring. Healthcare practitioners and individuals alike should maintain vigilance in remaining current with the latest dietary guidelines and the evolving body of research in this field. The success of dietary strategies depends on patient education, motivation, and long-term adherence. The finding contribute to the growing body of knowledge on metabolic syndrome and has the potential to make a significant impact on public health by reducing the prevalence and burden of metabolic syndrome and its associated complications.

Authors Contribution

Conceptualization: ZA, HS, MH

Writing-review and editing: ZA, HS, EA, MK, MW, TS, MAK, STM, HH

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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