Metabolic syndrome and possible treatments (consecutive therapies): a literature review

Abstract. Metabolic syndrome (MS) is defined by a cluster of risk factors including insulin resistance, hypertension, dyslipidemia, and obesity. Metabolic syndrome is also defined as having at least three metabolic risk factors — increased blood pressure, high blood sugar level, excess body fat, and abnormal cholesterol levels — and greatly increases the chance of future cardiovascular problems. The last 50 years have seen a dramatic increase in metabolic disorders, including obesity and type 2 diabetes, with the number of individuals diagnosed with type 2 diabetes worldwide expected to surpass 360 million by 2030. Early diagnosis is important in order to employ effectively lifestyle and risk factor modification. Pharmaceutical therapy in MS is aimed at treating the individual components of MS such as antihypertensives, statins, and metformin. Some natural compounds, Yoga and dietary elements. Therefore in this article various therapies (possible treatments) were reviewed. The world is in emergent need for searching of treatments for metabolic syndrome. The MS is a constellation of common metabolic disorders that is associated with type 2 diabetes and cardiovascular disease. Insulin resistance and dyslipidemia play central roles in the pathophysiology of this syndrome. In this modern world, metabolic syndrome is reaching epidemic proportions. 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. 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. Pharmacological treatment is only based on only diagnosis and symptoms. Recently approved anti-obesity drugs can be prescribed to reduce body weight, particularly abdominal visceral fat. A first line intervention targeting MS involves dietary and lifestyle modification with regular physical activity over a period of time. However, improvement in MS parameters can only be maintained when these modifications can be sustained. Therefore, dietary and lifestyle modification in continuum is required to overcome MS holistically. The main and foremost treatment for metabolic syndrome is to eliminate the causative risk factors of it.

Keywords: diabetes; non communicable diseases; treatment and metabolic syndrome

Introduction

Disease patterns around the globe are undergoing rapid structural changes over the last three decades, with a sudden increase in the burden of Non-Communicable Diseases (NCDs) and a decreasing trend of communicable diseases [1]. The Global Burden of Disease study, brings to light this phenomenon of epidemiological transition in India, with a 62.7 % of the total mortality in 2016 contributed by the NCDs. Key elements contributing to the development of these NCDs have been identified and are studied together under the heading of Metabolic Syndrome (MS) [2].

The last 50 years have seen a dramatic increase in metabolic disorders, including obesity and type 2 diabetes mellitus (T2DM), with the number of individuals diagnosed with T2DM worldwide expected to surpass 360 million by 2030 [3]. This prevalence is rising given the epidemic of obesity, which is fueled, in part, by physical inactivity and unhealthy eating patterns [4]. A recent study from the United States reported the prevalence of MS to be around 22.9 % [5]. A study conducted in the eleven large urban cities of India during 2006–2010 reported the prevalence of MS as high as 35 % [6]. P.M. Khatri et al. concluded the prevalence of an MS diagnosis was alarmingly high among the population of women in higher socioeconomic class of Bikaner (Rajasthan) [6].

MS is defined by a cluster of risk factors including insulin resistance, hypertension, dyslipidemia, and obesity [7]. MS is also defined as having at least three metabolic risk factors — increased blood pressure, high blood sugar level, ex-

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cess body fat, and abnormal cholesterol levels — and greatly increases the chance of future cardiovascular problems [8]. The symptom cluster that defines the MS has been shown to contribute to the pathogenesis and progression of T2DM and its related disorders, cardiovascular disease (CVD), and other chronic conditions [9–11]. Increased sympathetic activity and reduced parasympathetic tone have been implicated in the pathogenesis of the MS and its related complications. In addition, there is mounting evidence that chronic psychological stress and negative mood states are strongly associated, in a bidirectional manner, with insulin resistance, glucose intolerance, central obesity, dyslipidemia, hypertension, and other components of the MS [12, 13]. This prevalence is rising given the epidemic of obesity, which is fueled, in part, by physical inactivity and unhealthy eating patterns [14]. Given the dramatically increasing prevalence, associated premature mortality, disability, complications, and social and economic costs, management of the metabolic syndrome is of importance to public health. Here, we review the epidemiology and summarize existing therapies for MS.

Methodology. Relevant studies were identified and extracted by irrespective of time and a comprehensive search in database search engines namely Pub Med, Scopus, Science Direct and Google Scholar. Irrelevant studies were excluded in this review article. Terms were typed and searched as “metabolic syndrome, treatments, dyslipidemia and Yoga” in titles, abstracts and keywords.

Epidemiology. Worldwide prevalence of MetS ranges from < 10 % to as much as 84 %, depending on the region, urban or rural environment, composition (sex, age, race, and ethnicity) of the population studied, and the definition of the syndrome used (table 1) [15]. A.J. Cameron et al. have concluded that the differences in genetic background, diet, levels of physical activity, smoking, family history of diabetes, and education all influence the prevalence of the MS and its components [16]. Y.W. Park et al. noticed that there is an increase in the prevalence of MS from 20 years old through the sixth and seventh decade of life for males and females, respectively [17]. L. Palaniappan et al. concluded that each 11 cm increase in waist circumference is associated with an adjusted 80 % increased risk of developing the syndrome within 5 years [18]. The prevalence of MS among adult population in India was 30 %. State wise analysis of MS showed that the maximum prevalence of MS was reported in Madhya Pradesh (50 %) followed by New Delhi (43 %), Odisha (43 %) and Telangana (42 %). Least pooled prevalence of MS was found in Jammu & Kashmir (15 %) followed by Haryana (18 %) and Punjab (21 %) [19].

### Table 1. Diagnosis of Metabolic Syndrome by ATP III Criteria [20]

| Condition                            | Criteria                                      |
|--------------------------------------|-----------------------------------------------|
| Increased abdominal waist circumference | > 40 inches in men                           |
|                                      | > 35 inches in women                          |
| Hypertriglyceridemia                 | ≥ 150 mg/dl                                   |
| Low HDL                              | > 40 mg/dl in men                            |
|                                      | > 50 mg/dl in women                           |
| Hypertension                         | ≥ 130/85 mmHg                                 |
| Fasting glucose                      | ≥ 100 mg/dl                                  |

Possible treatments of Metabolic Syndrome

Lifestyle modification

Increasing physical activity helps with weight reduction. It additionally has beneficial effects on metabolic risk factor. Beyond weight ability to control and decrease of aggregate calories, the eating regimen diet should be low in soaked fats, Trans fats, cholesterol, sodium, and straightforward sugars. Compelling weight reduction requires a mix of caloric confinement, physical movement, and inspiration; successful long lasting support of weight reduction basically requires a harmony between caloric admission and physical action.

Exercise. Reduced daily physical activity in healthy young adults is associated with negative metabolic consequences such as decreased insulin sensitivity and increased abdominal fat [21]. Therefore increased physical activity is likely to be the evolutionary favored pathway to prevent the development of insulin resistance during metabolic derangements. Chronic subclinical inflammation associated with the MS could be one reason for the continued physical inactivity and the induction of a vicious cycle. J. Gustat et al. showed a strong association between obesity and physical inactivity [22]. There is an inverse relationship between physical activity, body mass index (BMI), hip-waist ratio, and waist circumference [23–25].

So maintaining an active lifestyle can prevent the development of the MS. Maintaining lean body mass is essential for better glucose transport and fat metabolism. Reduction in fat mass is helpful in increasing adiponectin levels and improving cytokine profiles; changes in adipokines and cytokines are associated with the MS. Controlling the release and activity of at least two cytokines, TNF-α and interleukine-6 (IL-6), could contribute to the natural protective effects of physical activity. IL-6 is the first cytokine to be released into the circulation during exercise, and its levels increase in an exponential fashion in response to exercise [26]. IL-6 acts as both a proinflammatory and anti-inflammatory cytokine. When secreted by T cells and macrophages, IL-6 stimulates the immune response and boosts inflammatory reactions, while muscle-produced IL-6 exerts anti-inflammatory effects through its inhibitory effects on TNF-α, IL-1β, and activation of interleukin-1 receptor antagonist (IL-1ra) and IL-10. Exercise also confers protection against TNF-induced insulin resistance [27, 28]. At least two distinct pathways are involved in glucose transport; one is stimulated by insulin or insulin mimetics and the other is activated by contraction or hypoxia [29, 30]. Phosphatidylinositol 3 kinase is involved in insulin activated (but not contraction-activated) pathway, while 5’AMP-activated protein kinase participates in contraction-activated reactions [31, 32].

Yoga

Yoga is rooted in Indian philosophy and has been a part of traditional Indian spiritual practice for millennia [33]. Yoga traditionally is a complex intervention that comprises not only physical activity, but also advice for breathing exercises, meditation and advice for a healthy and ethical lifestyle. While the ultimate goal of traditional yoga has been described as unifying mind, body and spirit, it has become a popular means of promoting physical and mental well-being [34]. Yoga, in Sanskrit means ‘Yuj’ meaning to unite the mind,
body, and spirit. Yoga an ancient science has its roots in the Indus valley civilization dating back to 5000 BC. Ashtanga Yoga the eight limb Yoga is from the ancient text Patanjali Yoga Sutras, which is widely regarded as the authoritative text on Yoga. Yoga helps in maintaining the body physically fit. To reduce the risk of the MS physical fitness is necessary. Several methods are there in yoga. Some of them are Asanas, Pranayamas, Kriyas. The Asanas which prevent the diabetes are Suryanamaskaras, Arathmysrendrasana, Paschimottana, Hamsa, Mayura, Jatarijparavartana asana. Pranayamas include Suryabhedhana, Chandra Bhedana, Seethli, Seetkari, Brahmani, Bastrika, Nadisodhana. It brings balance to the physical, mental, emotional, and spiritual dimensions of the individual. Yoga is a holistic lifestyle that includes all components of healthy lifestyle. Yoga is based on five basic principles: proper relaxation, proper exercise, proper breathing, proper diet, positive thinking and meditation [35]. Glucose toxicity, caused by chronic hyperglycemia, is a potential precursor for T2DM. Some studies concluded that yoga only significantly lowered FPG in evening sessions in diabetic groups, and that it was ineffective for the non-diabetic males and morning session groups of both the genders [36, 37]. Yoga exercise for 16 weeks in obese postmenopausal women has been shown to improve serum lipids, adiponectin levels and MS risk factors. It is also reported that a three-month yogabased lifestyle program for patients with T2DM can reduce the co-morbidity of dyslipidemia [38, 39]. A recent literature also suggests that one-year yoga practice is beneficial in reducing central obesity by modulating ghrelin in the plasma [40].

Yoga practice has been shown to reduce the concentration of adipose cells in the visceral region, thus attenuating or minimizing excess free fatty acid (FFA) released from adipose cells [40, 41]. This can improve muscle cell, leucocyte and adipocyte-mediated glucose uptake by affecting the receptor composition of their plasma membrane, thereby reducing circulating glucose levels and increasing insulin sensitivity [42]. This can also minimize the loss of the pancreatic cells’ ability to produce sufficient insulin by reducing prolonged FFA concentration and its resultant lipotoxicity [43]. In line with this, reduced FFA secretion from visceral adipocytes, reduced access of FFA to the liver through splanchnic circulation and improved gluconeogenesis and glycosynthesis have been reported in diabetes patients in response to yoga [42, 43]. The reduced number of abdominal fat cells indicates shrinkage of an inflammatory cell infiltration site, which may result in turning down the release of proinflammatory mediators such as tumor necrosis factor-α and interleukin-6 [44]. This, along with increased adiponectin production from the metabolically healthy adipocytes, may alleviate the proinflammatory mediators, lower oxidative stress and reduce the chance of insulin resistance [45]. On the other hand, yoga may also improve growth hormone levels and improve sex steroid hormone levels, which help to normalize LDL and HDL levels by diminishing excessive hepatic TG accumulation [46, 47]. Rejuvenation/regeneration of cells of pancreas due to abdominal stretching during yoga exercise, which may increase utilization and metabolism of glucose in peripheral tissues, liver, and adipose tissues through enzymatic process [48]. More active practices followed by relaxing ones lead to deeper relaxation than relaxing practices alone, documented by research from Swami Vivekananda yoga research foundation near Bangalore city and possibility of neuroplasticity bringing about changes in the pituitary-pancreatic axis [49]. Muscular relaxation, development and improved blood supply to muscles might enhance insulin receptor expression on muscles causing increased glucose uptake by muscles and thus reducing blood sugar [50]. The improvement in the lipid levels after yoga could be due to increased hepatic lipase and lipoprotein lipase at cellular level, which affects the metabolism of lipoprotein and thus increase uptake of triglycerides by adipose tissues [51]. Pranayama practices, stretches the lung tissue producing inhibitory signals from action of slowly adapting receptors and hyperpolarising currents. These inhibitory signals coming from cardiorespiratory region involving vagi are believed to synchronize neural elements in the brain leading to changes in the autonomic nervous system; and a resultant condition characterized by reduced metabolism and parasympathetic dominance [52]. Yoga and pranayamas seems to influence through modifying activity of ascending reticular activating system and thereby also interact with autonomic centers in the brainstem thus affecting cardiorespiratory and metabolic parameters [53].

**Diabetic modification.** Unhealthy dietary patterns and sedentary lifestyles have led to a notable increase in the prevalence of overweight and obesity worldwide. Non-communicable chronic diseases (NCDs) related to unhealthy dietary patterns and weight gain have expanded in parallel, being the major cause of morbidity and mortality both in developed and underdeveloped countries [54]. N. Steckhan et al. analyzed the positive effects of different dietary approaches on MS inflammatory markers [55]. J. Godos et al. also conducted a meta-analysis to demonstrate the preventive role of the promotion of healthy dietary patterns to reduce the prevalence of MS [56]. Recent evidence supports the implementation of healthy food-based dietary interventions instead of calorie or isolated nutrient restriction diets [54]. 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 MS has been observed through many studies [57, 58]. 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 [59]. Various dietary interventions have shown significant weight loss, improvement in the MS components, improvement in body composition and cardio-metabolic fitness [57, 60]. 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 MS. 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 hypertriaecglycerolemia (p < 0.001) were seen with the low carbohydrate (CHO) diet group [61]. Thus diet and lifestyle interventions are regarded as the first line of defense for combating the metabolic disorders.
Pharmacological treatments. 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 [62]. First-line recommendations for reducing Cardiovascular Heart Disease (CHD) risks include smoking cessation, reducing LDL-C levels, blood pressure, and glucose levels to recommended goals. LDL-lowering standard drugs are also recommended. These include statins and ezetimibe. Other newly identified drugs that reduce the level of progression of metabolic syndrome related disorders includes thiazolidinediones, GLP-1 agonists, and DPP-4 inhibitors. Statins are a class of drugs that in their active hydrolysed form are specific inhibitors of HMG-CoA reductase, the enzyme responsible for catalyzing the conversion of HMG-CoA to mevalonate, an early rate limiting step in the cholesterol biosynthesis pathway. Inhibition of HMG-CoA reductase with statins has been shown to reduce the plasma levels of cholesterol and apoB-containing lipoproteins in hypercholesterolemic models [63]. Statins have been shown to influence the secretion of both LDL and VLDL in patients with hyperlipidemia. More recently, statins were also found to be effective in reducing plasma TG levels, inhibiting intracellular cholesterol biosynthesis and upregulating LDL receptor expression [64, 65]. Ezetimibe was the first agent to selectively inhibit of biliary and dietary sterol absorption, without interfering with absorption of liposoluble nutrients. It acts by blocking the transmembrane protein discovered in 2004, Niemann-Pick C1-Like 1 (NPC1L1) from intestinal cells, with subsequent decrease of the cholesterol delivered to the liver, upregulation of LDL receptor expression and increase of cholesterol clearance. Experimental studies have involved NPC1L1 protein and a positive effect of ezetimibe in other physiopathological components of metabolic syndrome, as well [66]. Nicotinic acid is a classical broad-spectrum hypolipemiant, known to decrease LDL cholesterol and triglycerides and as the most effective in raising HDL-C level. Nicotinic acids have pleiotropic effects related to inhibition of lipolysis in the adipocytes and reduced triglycerides and exert many metabolic effects including anti-inflammation. It acts by blocking the transmembrane protein discovered in 2004, Niemann-Pick C1-Like 1 (NPC1L1) from intestinal cells, with subsequent decrease of the cholesterol delivered to the liver, upregulation of LDL receptor expression and increase of cholesterol clearance. Experimental studies have involved NPC1L1 protein and a positive effect of ezetimibe in other physiopathological components of metabolic syndrome, as well [66]. Nicotinic acid is a classical broad-spectrum hypolipemiant, known to decrease LDL cholesterol and triglycerides and as the most effective in raising HDL-C level. Nicotinic acids have pleiotropic effects related to inhibition of lipolysis in the adipocytes and reduced triglycerides and CRP synthesis [67]. Reduction in blood pressure using antihypertensive medications has been shown to reduce the risk of cardiovascular and cerebrovascular events and mortality. There is a recommendation to start using one out of five antihypertensive medications as first-line treatment: thiazides diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB) or a beta-blocker (BB) depending on the individual patients risk profile [68]. Considering experimental and clinical studies that have demonstrated the involvement of the rennin-angiotensin-aldosterone system in complex interactions between endothelial dysfunction, insulin resistance, and development of atherosclerosis, inhibitors of this system (RAAI), either ACEI or ARB, could have added metabolic benefits [68, 69]. Currently, seven types of antidiabetic medications; i.e., metformin, sulfonylurea, thiazolidinedione, dipeptidyl peptidase-4 (DPP-4) inhibitors, insulins, glucagon-like peptide 1 receptor agonists (GLP-1RAs) and sodium/glucose co-transporter 2 (SGLT-2) inhibitors, are available for treating T2DM, with metformin being first-line of treatment [70]. SGLT-2 inhibitors and GLP-1RAs improving the glycemic control and demonstrating potential CVD benefits, several other criteria of the metabolic syndrome including body weight/waist circumference, dyslipidemia and blood pressure also improved when treating with these drugs [71].

Conclusions

The metabolic syndrome is a constellation of common metabolic disorders that is associated with type 2 diabetes and cardiovascular disease. Insulin resistance and dyslipidemia play central roles in the pathophysiology of this syndrome. Patients diagnosed with metabolic syndrome often exhibit raised TG and LDL cholesterol, reduced HDL cholesterol and raised blood pressure and fasting plasma glucose. In this modern world, metabolic syndrome is reaching epidemic proportions. 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. 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. 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. Pharmacological treatment is only based on only diagnosis and symptoms. Recently approved anti-obesity drugs can be prescribed to reduce body weight, particularly abdominal visceral fat. Other medications such as TZDs, metformin, lipid-lowering medications, RAS blockers, and cilostazol exert many metabolic effects including anti-inflammation. A first line intervention targeting MS involves dietary and lifestyle modification with regular physical activity over a period of time. However, improvement in MS parameters can only be maintained when these modifications can be sustained. Therefore, dietary and lifestyle modification in current is required to overcome MS holistically. The main and foremost treatment for metabolic syndrome is to eliminate the causative risk factors of it.

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абілічний синдром і підходи до його лікування (послідовна терапія): огляд літератури

Резюме. Метаболічний синдром (МС) визначається кластером факторів ризику, включаючи резистентність до інсуліну, артеріальну гіпертензію, дисліпідемію та ожиріння. Метаболічний синдром також визначається як наявність щонайменше трьох метаболічних факторів ризику — підвищеного артеріального тиску, підвищеного рівня цукру в крові, надлишку жиру в органах і системах. Метаболічний синдром також визначається як наявність щонайменше трьох метаболічних факторів ризику — підвищеного артеріального тиску, підвищеного рівня цукру в крові, надлишку жиру в органах і системах. Метаболічний синдром також визначається як наявність щонайменше трьох метаболічних факторів ризику — підвищеного артеріального тиску, підвищеного рівня цукру в крові, надлишку жиру в органах і системах. Метаболічний синдром також визначається як наявність щонайменше трьох метаболічних факторів ризику — підвищеного артеріального тиску, підвищеного рівня цукру в крові, надлишку жиру в органах і системах.

Метаболічний синдром і підходи до його лікування (послідовна терапія): огляд літератури