



# Metabolic Syndrome: Cluster of Diseases

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## Abstract

Metabolic syndrome is cluster of diseases, having biochemical, physiological and clinical factors that directly escalate the menace of diabetes (type 2), dyslipidemia, hypertension, insulin resistance, endothelial dysfunctioning and cardiovascular diseases. Basically it is a chronic inflammation having characteristics of producing adipokines including tumor necrosis factor, interleukin 6, prothrombin activation inhibitor 1 and C-reactive proteins. These adipokines results in abdominal obesity by propagating into localized area which further cause oxidative stress, dysfunctioning in endothelial cells by exaggeration of blood coagulation, developing atherothrombotic and atherosclerosis conditions in body. Modification in dietary habits and lifestyle by including fiber rich foods and physical activity and positive role of polyphenol rich foods in the prevention of cardiovascular diseases, cancer, insulin resistance and diabetes showed great improvement in the severity of disease. This review provides quick understanding of metabolic syndrome definition, epidemiology, pathophysiology and treatment strategies.

**Keywords:** Metabolic syndrome, Diabetes, Heart diseases, Polyphenols, hypertension

## Introduction

Globally metabolic syndrome (MetS) is an accelerating clinical and public health challenge. In previous era, MetS was considered to be a concept instead of diagnosis [1]. Firstly, a Swedish physician Kylin highlighted this concept in 1920's by showing the linkage of high blood glucose, hypertension and gout [2]. After that in 1947 Vague exhibited that visceral obesity was commonly related to metabolic anomalies found in cardiovascular diseases (CVD) and diabetes [3]. In 1965 Crepaldi presented an abstract which highlights the strong association between hyperglycemia, high blood pressure and obesity at the European Diabetes annual conference [4].

With the passage of time interest of scientists had increased in the field of MetS and they started given their theories about it. In 1988 Reaven called MetS as Syndrome X and its concept basically was related to insulin resistance [5]. However, in 1992, it was again renamed The Insulin Resistance Syndrome [6]. Foremost reason in the enhancement MetS trend in urbanization is the use of excessive intake of calories and physical inactivity which further lead towards overweight and obesity. Diabetes and cardiovascular diseases increased the risk of developing MetS 2 times and 5 times respectively [7]. Moreover, if patients facing the issue of MetS they are already 2 to 4 times at risk of

developing stroke and 3 to 4 times heart attack. Patients having MetS are 2 folds more prone towards deaths as compared to those who have not suffered from it [8,9]. MetS has many definitions, but the most important is the one used from World Health Organization (WHO) developed in 1999. According to WHO, confirmation of MetS is established using abnormal laboratory results including glucose intolerance, hypertension, lipid profile and atherogenesis [10]. However, the International Diabetes Federation (IDF) suggested a new definition of the MetS in April 2005. MetS is cluster of diseases, having biochemical, physiological and clinical factors that directly escalate the menace of diabetes (type 2) and cardiovascular diseases [11,12]. Prevalence of metabolic syndrome varies drastically around the globe, both on a country by country basis and at smaller regional levels such as rural, suburban, and urban. Since the 20th century, most countries have seen an increase in the prevalence of metabolic syndrome in the population. Extensive studies have been completed to track the development of the disease in the United States and China. Other countries, such as Malaysia, India, Philippines, Nigeria, Brazil, Turkey, and Iran have also observed metabolic syndrome in greater than 25% of the population [13]. Main contributing factors in the prevalence of metabolic syndrome are high socioeconomic status, decreased physical activity in daily life, genetics, and smoking and high body mass index [14]. Study conducted by Ponzolzer et al., demonstrated that prevalence of metabolic syndrome among postmenopausal women were ranges from 33-42% [15]. Results of another study, exhibited that when the person gain 2.5kg weight over the period of 17 years the risk of developing MetS increased by 45% [16]. Palaniappan et al., showed that when the waist circumferences of individual increased ten cm from normal range, then an increase in MetS prevalence in means of 80-90% was noticed in a shorter period of time [17]. In Pakistani population, obesity in terms of waist circumference is ranges from 45-68%, with a strong relationship found between arm fat and insulin resistance. Hypertriglyceridemia and dyslipidemia are present in the 28-55% of general population, while 67-81% has decreased levels of high density lipoprotein (HDL). Fifty percent were found to be at high risk of metabolic syndrome due to hypertension. With

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the increased prevalence of all these metabolic risk factors, the occurrence of metabolic syndrome in Pakistan according to various definitions is reported to be from 17 to 48% [18].

### **Pathophysiology of metabolic syndrome**

MetS is basically chronic but minute inflammation in body that occurs due to the strong association between modifiable and genetic factors which constitutes the metabolic syndrome (Figure 1).

### **Obesity**

It is considered to be the chief cause of MetS results due to the higher consumption of calorie rich foods and decreased physical activity in daily life. When there is an excessive fat in the body, it is stored in adipose tissues resulting in hypertrophy of adipocytes (fat storing cells) [19]. Enlargement in fat storing cells reduce the supply of blood towards them and increased the rate of hypoxia in that region of adipocytes [20]. Due to hypoxia, excessive production of adipokines, including free fatty acids, tumor necrosis factor alpha, interleukin-6, C reactive proteins and plasminogen activator inhibitor-1 [21]. These adipokines results in abdominal obesity by propagating into localized area, which further cause oxidative stress [22], dysfunctioning in endothelial cells by exaggeration blood coagulation, developing atherothrombotic and atherosclerotic conditions in body [23]. Greater level of adipocytes, increased the amount of free fatty acids in abdominal region of human body, which cause the insulin resistance by altering the function of pancreatic beta cells [24]. Free fatty acids also increase the amount of plasminogen activator inhibitor-1 [25].

### **Tumor Necrosis Factor- $\alpha$ (TNF- $\alpha$ )**

It consists one of the important adipokines, which reduces the beta cell sensitivity [21] by apoptosis of fat storing cells. This action of TNF- $\alpha$  leads to the formation of free fatty acids. This factor has strong positive association with waist circumference, body weight and high level of triglycerides, while it is associated negatively with high-density lipoproteins (HDL) [26].

### **C-Reactive Protein (CRP)**

It considered being a strong independent predictor for the identification of the metabolic syndrome. High level of CRP in blood is positively associated with waist circumference [27], increased blood sugar level and insulin resistance [28]. It also predicts the initiation of heart disease and related events later in life [29]. Interleukin-6 is an important determinant of CRP, having both anti-inflammatory and inflammatory characteristics.

It is found in both skeletal and adipose tissues [30]. In its excess release it inhibits the proper functioning of enzyme called lipo-protein lipase. It plays an important role in the development of diabetes, having negative association with HDL [31].

### **Prothrombin activator inhibitor 1 (PAI-1)**

This inhibitor has strong association with enzyme called protease. PAI-1 suppresses the plasminogen activator, which further alters the fibrinolysis leading to atherothrombosis

[32]. High levels of PAI-1 are reported in obese individuals as compared to non-obese [33].

### **Leptin**

It is a satiety hormone which suppress the appetite and prevents from obesity in normal individuals. In obese person's resistance in leptin receptors has been increased that fails to give signals to pathway which suppresses continues eating and individual starts to gain higher weight or body mass index [21,34]. It is not only involved in the development of obesity, but leptin is a basically nitric oxide dependent vasodilator which enhances the activity of sympathetic nervous system mainly in the kidneys. Therefore, blood pressure of human body is increased [35]. In simple words researchers demonstrated that leptin resistance has been associated with obesity, high blood pressure and heart diseases [36]. Obese individuals display also insulin resistance [37]. Insulin resistance disturbs all the events of glucose metabolism, resulting in the elevation of blood glucose (hyperglycemia) [38]. It also affects exogenously induced insulin in body, by reducing its action or response in muscle, adipose and liver. To cope with hyperglycemia, beta cells of pancreas secretes more insulin. If this conditions continuously prevails in the body, then hyperglycemia shifts towards another serious ailment called type II diabetes, which is the main inducer of metabolic syndrome [39,40].

### **Insulin**

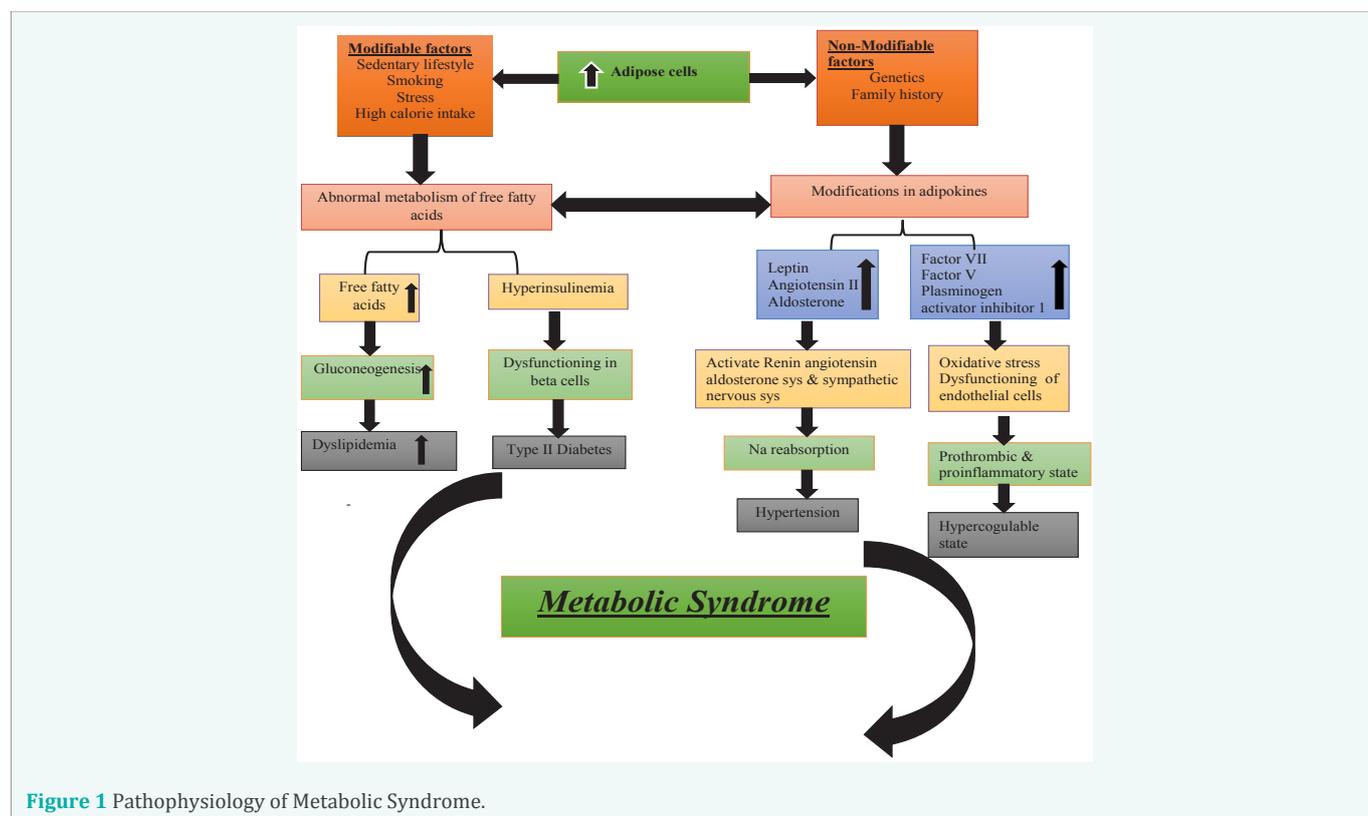
Role of insulin in body starts by its binding with insulin receptors, in the presence of elevated levels of glucose. After binding to receptor insulin initiates the functioning of two pathways named as, phosphoinositide 3-kinase (PI3K) and mitogen activated protein kinase (MAP). Due to the disturbance in insulin activity PI3K is affected while the other one remains in its normal processing. Alterations in PI3K lead towards dysfunctioning of endothelial tissues by reducing nitric oxide production, mainly in obese individuals as compared to normal adults [41].

### **Hypertension**

Studies exhibited that hyperglycemia and hyperinsulinemia are involved in the development of hypertension, by triggering the renin angiotensin system (RAS) and enhancing the action of angiotensin II (AT-II) [42]. In this condition kidneys start to reabsorb more sodium and increase the vasoconstriction in arteries surrounding heart, which lead towards increased levels of blood pressure. Some other studies also demonstrated the release of aldosterone by the activation or over expression of AT-II [43]. Aljada et al., demonstrated that individuals whose dietary intake of fatty foods is higher, display positive relation with oxidative stress and inflammation as compared to those who have higher intake of fruits and vegetables or lower calories [44,45].

### **Treatment strategies of metabolic syndrome**

Management of metabolic syndrome is very important to reduce the risk of related diseases [46]. Key approaches to overcome the burden of metabolic syndrome includes alteration



**Figure 1** Pathophysiology of Metabolic Syndrome.

in lifestyle by adopting multidisciplinary team approach (Table 1) such as dietitian, physician, diet, exercise, behavioral specialists and medicines [47]. Joint work of all these practitioners for modification of the severity of metabolic syndrome, showed positive results [48]. Weight control by reducing 500 calories/day is another strategy for treating metabolic syndrome. Results of various researches recommend that 10% weight reduction of the individuals having MetS, is associated with a decrease of its rate by 20% [49]. Drop in the weight is also positively linked with the triglycerides decline while it is negatively associated with HDL, hypertension and insulin resistance [50-52]. Mediterranean diet has shown positive influence on metabolic syndrome by decreasing levels of LDL and triglycerides [53]. Dietary Approaches to Stop Hypertension (DASH diet) improves the blood pressure in individuals suffering from MetS [50]. It provides the recommendation of fat intake in the level of 25-30% of total calories and intake of cholesterol not more than 200mg/day [54]. Protein intake should be in moderate quantities, because excessive protein intake has serious effect on human kidneys and alter their normal functioning. Recommended intake of protein is 10-20% of total calories. Meal replacement is another effective strategy to overcome disease burden. Junk fast foods trends should be shifted towards conventional home made foods with lower calories. Limited intake of sugar and salt is also recommended [55]. Increase intake of foods rich in potassium, magnesium and non-unsaturated fatty acids decreased the risk of developing MetS [56] by improving the symptoms of dyslipidemia, insulin resistance and blood pressure. Recommended intake of fiber is 25-35g/day, in order to lower the risk of MetS [57]. Physical

activity has also negative association with MetS and daily activity of 30 minutes is recommended to attain balance routine [58]. Results of different researches indicated that if a person targets itself to consume 500 calories per day by physical activity then it lowers the risk of the disease by 20%. Brisk walk is suggested to be the best activity that lowers the LDL from body and raises the levels of HDL in body [59].

Nowadays flavones and flavonols are primarily focused by researchers in the prevention of cardiovascular ailments [60]. Results of ten studies exhibited that consumption of phenolic compounds (Table 1) including flavonols, anthocyanin, flavanones and flavones decreased the risk of developing heart diseases [61]. Another study showed that individuals (42,000) who followed a diet rich in phenolics secure their health from death by 30% [62]. Spanish branch of the European and McCullough et al., (2012) stated that mortality rate due to heart diseases decreased by the fair consumption of flavonoids. The consumption of food rich in polyphenol food matrices improves the resistance to oxidative modification of LDL in humans, and this effect can be explained by the quick incorporation of phenolic acids in LDL [63]. Although the role of polyphenols in CVD risk is still controversial, the majority of epidemiological and intervention studies indicate a decrease in LDL cholesterol concentrations, increased in HDL cholesterol concentrations, and a resistance of LDL to oxidation following the intake of polyphenolic-rich foods in healthy humans [64-66]. Siasos et al., (2014) reported that consumption of grape juice for 2 weeks improves the heart functions in twenty-five smokers [67]. Similar results were elaborated by the Barona et al., (2012) who describe that intake of grape juice for longer



**Table 1:** Multi-disciplinary approaches to overcome metabolic syndrome.

<b>Assessment</b>	Waist circumference <0.8 for women and <0.9 for male BMI must be in the range of 18.5-24.5
<b>Diet</b>	Increase intake of fruits and vegetables Decreased intake of sugar, salt, saturated fatty acids and beverages Total calories from fat and protein 25-35% and 10-20% respectively Daily intake of fiber 25-35 g/day
<b>Physical activity</b>	Daily activity of 30 minutes lowers the risk of developing diabetes, hypertension and CVD Burn 500 calories/day to achieve optimum goal Focus brisk walk for increasing HDL in body
<b>Medicines</b>	Appetite suppressants e.g. orlistat, sibutramine etc. inhibit the intake of food Increase stool episodes Increase fat excretion

duration reduce the endothelial dysfunctional properties in men having metabolic syndrome [68]. Scientists believed that resveratrol is the main reason for the improvement in endothelial functions [69]. In addition to the effect of phenolic compounds on heart, varied range of studies also exhibited their beneficial effect on blood lipid profile. Several studies support this aspect i.e. one study indicated that intake of red wine for thirty-five days by the men who were at risk of developing cardiovascular diseases. After the study had ended results showed the positive association between red wine intake and high density lipo-protein level [70] and negative association with low density lipo-proteins [71]. Many studies also highlight the importance of cocoa phenolics in lowering the blood pressure [72]. Effect of flavan 3-ol cocoa had been observed in twenty randomized controlled trials and results demonstrated that these products significantly lower the blood pressure. They also improve the endothelial and heart vasomotor functions by reducing the plasma nitric oxide in smokers and in patients with heart failure respectively [73]. A meta-analysis of forty randomized studies demonstrated that cocoa phenolics improved the HDL concentration by 0.05 mM by decreasing the 0.08 mM of LDL ratio [74]. On the other side berry compounds possibly enhance HDL levels in the body [75]. The tumorigenesis and carcinogenesis predominantly in the gastrointestinal tract can be affected by phenolic constituents, reviewed in many epidemiological studies. A decrease in colorectal cancer has been related to the consumption of flavone, anthocyanin (procyanidine), flavonols and flavan-3-ol isoflavones. There is no clear suggestion between consumption

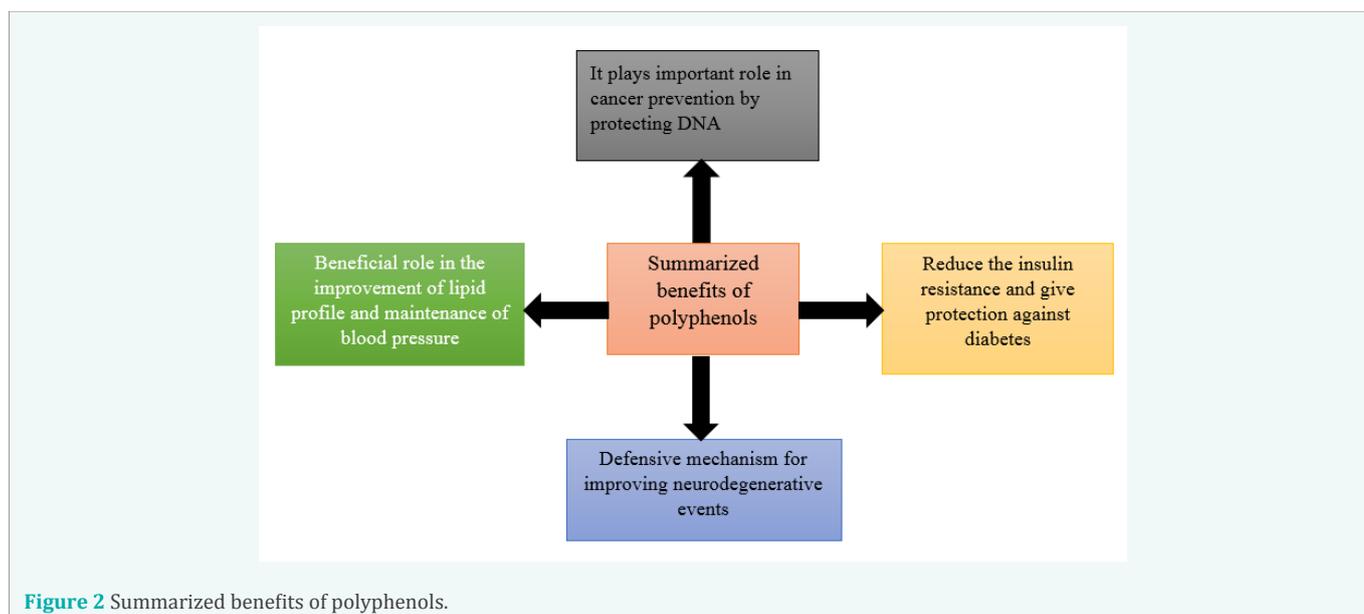
of flavonoids and decreased possibility of stomach and colorectal cancer [76].

The chemoprotective properties of tea and fruits have been also studied (Table 2). For example, short term intervention studies showed the preventive effects against carcinogenesis of polyphenols present in green tea. A study found that only one tumor was diagnosed among 30 subjects, who took green tea capsules (600mg of flavan-3ols/day) for 1 year, versus 9 cancers was diagnosed in the same sized control group [77]. Furthermore, the 4 weeks study on heavy smokers concluded that the number of damaged cells was reduced by the intake of five cups of green tea per day (400-500mg of flavan-3-ols per cup), by triggering the apoptosis and cell growth arrest. Hakim et al., (2012) found that the consumption of phenolics in green tea for 4 months (4 cups/day, 146 mg total/cup) reduced the urinary level of biomarker of oxidative DNA damage, 8- hydroxydeoxyguanosine [78]. A 12 weeks randomized, placebo-controlled study showed that the patients with high risk oral premalignant lesions, took green tea extracts (500, 750, or 1000mg/m<sup>2</sup>) and did not indicate any changes in tumor occurrence [79]. Though, FDA claimed that there are no or little sound scientific evidences to support the qualified health claims about intake of green tea and decreased incidence of gastric, colorectal, ovarian, prostate/breast and esophageal cancer.

Conversely, there are the studies which concluded that the consumption of blackcurrant juice for 3 weeks (666ml/day, 397 mg anthocyanin/day) and cranberry juices for 2 weeks (750ml/day) have no effect on oxidation of DNA [80]. Similarly, Giovannelli et al., (2011) investigated that procyanidin-rich-de-alcoholized wine (500ml/day) which contained 7 mg procyanidins/kg body weight have no effect of DNA damage after 4 weeks trial. The reduction in oxidative damage to DNA and chemo-preventive effect of berries has been associated in many human intervention studies [81]. Contrary to this, a recent trial displayed the preventive effect of rosemary and citrus extracts (daily consumption of 250mg, orally), through 37 % increase in the minimal erythema dose (MED) after 8 weeks, and stronger MED (56%) after 12 weeks [82]. However, more studies are required in order to support the alleged protecting effects, via appropriate and clinically significant conclusion facts. The relation between olive oil and its effect against carcinogenesis has also been investigated. For this, intake of virgin olive oil and urinary excretion of ethno-DNA adducts were studied, concluding insignificant differences between baseline and after intake of highest phenolic content 150mg/kg [83]. Dietary polyphenols

**Table 2:** Health claims of polyphenols in reducing metabolic syndrome.

Health Claims	Mechanism	References
Cardiovascular Diseases	Decrease LDL, increase HDL, Improve endothelial dysfunction, Reduce blood pressure	Wang et al., 2014, Lim, 2012, Siasos et al., 2014, Risoetal, 2013.
Cancer Insurgence	Decrease proliferation rate, Enhance apoptosis of damaged cells Reduced oxidative damage to DNA	Gonzalez et al., 2012, Woo and Kim, 2013, Hillestorm et al., 2006, Giovannellietal, 2011.
Diabetes	Reduce insulin resistance & HbA1c, Increase glucose metabolism, Improve vascular functioning	Xiao and Hogger, 2015, Cao and Wang, 2017



**Figure 2** Summarized benefits of polyphenols.

provide protection against type 2 diabetes by giving protection of beta cells from glucose toxicity, antioxidant and anti-inflammatory effects. Polyphenols rich diet inhibits the insulin resistance and enhances the functioning of beta cells of pancreas [84]. Polyphenols from coffee, guava tea, olive oil, chocolate, red wine, grape seed, and cocoa have shown anti-diabetic effects in type 2 diabetic patients by increasing glucose metabolism, improving vascular function, and reducing insulin resistance and HbA1c. Anthocyanin exhibited antidiabetic property by reducing blood glucose and HbA1c, increasing insulin secretion, and improving insulin resistance [85]. Data on the effects of long-term chronic consumption of flavan-3-ols on cardio-metabolic health are scarce. In a randomized, placebo-controlled trial in 93 patients with T2D, the intake of 7 grams per day of flavonoid-enriched chocolate (containing 850 mg flavan-3-ols and 100 mg isoflavones) for 1 year significantly improved insulin resistance. In this long-term trial, effects on hemoglobin A1c (HbA1c) and glucose were not observed. However, the authors acknowledged that the dropout rate was high and limited to postmenopausal women receiving diabetes therapy. In another study that only considered clinical trials conducted among non-Asian per-menopausal or postmenopausal women, soy isoflavones supplements for 3 months to 2 years significantly reduced serum insulin [86]. Benefits of polyphenols are summarized in Figure (2).

If a person is not able to achieve the targeted goal then physician suggest pharmacological approach. Appetite suppressants are mainly used and the most common is orlistat which decreases the absorption of fat by increasing stool frequency. Anti-obesity drugs must be used in moderation because these drugs display many side effects, including decrease of tolerating power of the body [87].

## Conclusion

MetS is a cluster of diseases, having biochemical, physiological

and clinical factors that directly escalate the menace of diabetes (type 2), dyslipidemia, hypertension, insulin resistance, endothelial dysfunctioning and cardiovascular diseases. Alterations in lifestyle remain the main intervention of choice for this population. Modern lifestyle modification therapy combines specific recommendations on diet and exercise with behavioral strategies. Pharmacological treatments should be considered for those whose risk factors are not adequately reduced with lifestyle changes. A realistic goal for overweight/obese persons is to reduce the body weight by >7% to 10% over a period of 6 to 12 months. Weight reduction should be combined with a daily minimum of 30 minutes of moderate-intensity physical activity. Nutritional therapy calls for a low intake of saturated and total fat intake; reduced consumption of simple sugars and high glycemic index foods; and increased intakes of fruits, vegetables, legumes, and whole grains. Statins can be combined with fibrates and niacin to achieve the target levels of LDL, triglycerides, and HDL. All these approaches have positive impact on reducing the severity of metabolic syndrome and improve the human health.

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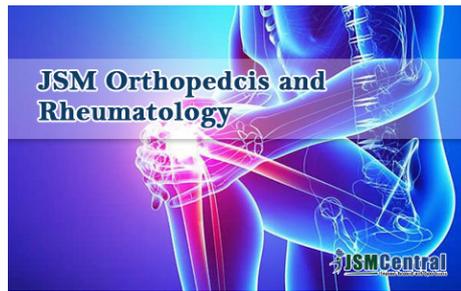
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