Review Paper

Metabolic Syndrome: An Emerging Threat

Rahman QAA[1], Razzak MA[2], Wahab MA[3]

DOI: https://doi.org/10.3329/jafmc.v14i2.45911

Abstract

Metabolic syndrome (MetS) is a multifaceted syndrome, which occurs frequently in the general population. It represents a cluster of metabolic abnormalities that include hypertension, central obesity, insulin resistance, and atherogenic dyslipidemia, and is strongly associated with an increased risk for developing diabetes and atherosclerotic and nonatherosclerotic cardiovascular disease (CVD). The pathogenesis of MetS involves both genetic and acquired factors that contribute to the final pathway of inflammation that leads to CVD. MetS has gained significant importance recently due to the exponential increase in obesity worldwide. Early diagnosis is important in order to employ lifestyle and risk factor modification. Here, we review the epidemiology, diagnostic criteria, pathogenesis and disease associations of MetS, and summarize existing management modalities.

Key-words: Metabolic syndrome, CVD, Insulin resistance, obesity, Dyslipidemia, Hypertension.

Introduction

The Metabolic Syndrome (MetS), also known as 'insulin resistance syndrome', 'syndrome X', 'hypertriglyceridemic waist', and 'the deadly quartet'[1] is a constellation of an interconnected physiological, biochemical, clinical, and metabolic factors that directly increases the risk of atherosclerotic cardiovascular disease (ASCVD), Type 2 Diabetes Mellitus (T2DM)[2,3]. The diabetes consultation group of the World Health Organization (WHO)[4] created the first internationally recognized definition of MetS in 1998. They defined MetS as the presence of insulin resistance (impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes mellitus) in addition to two of the following risk factors: obesity (waist-hip ratio or body mass index), hyperlipidemia (hypertriglyceridemia, low high-density lipoprotein [HDL] cholesterol), hypertension or microalbuminuria[1].

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 used5,6. In general, the International Diabetes Federation (IDF) estimates that one-quarter of the world's adult population has the MetS[7]. Higher socioeconomic status, sedentary lifestyle, and high body mass index (BMI) were significantly associated with MetS. According to National Cholesterol Education Programme Adult Treatment Panel III (NCEP-ATP III) criteria, 2001 the prevalence of MetS varied from 8% to 43% in men and from 7% to 56% in women around the world[8]. Ponholzer et al. reported that there is high prevalence of MetS among postmenopausal women, which varies from 32.6% to 41.5%[9]. A Framingham Heart Study report indicated that a weight increase of ≥2.25 kg over a period of 16 year was associated with up to 45% increased risk of developing the MetS[10], and it has been shown by Palaniappan et al. that each 11 cm increase in waist circumference (WC) is associated with an adjusted 80% increased risk of developing the syndrome within 5 years[11]. MetS confers a 5-fold increase in the risk of type 2 diabetes mellitus (T2DM) and 2-fold the risk of developing cardiovascular disease (CVD) over the next 5 to 10 years[12]. Further, patients with the MetS are at 2- to 4-fold increased risk of stroke, 3- to 4-fold increased risk of myocardial infarction (MI), and 2-fold the risk of dying from such an event compared with those without the syndrome[13] regardless of a previous history of cardiovascular events[14].

Diagnostic Criteria

Since the initial description of MetS, several iterations of this definition have been proposed[1] (Table-I). The most commonly used criteria for definition at present are from the WHO[15], the European Group for the study of Insulin Resistance (EGIR)[16], the NCEP ATP III[17], American Association of Clinical Endocrinologists (AACE)[18], and the IDF[19].

Table-I: Diagnostic criteria proposed for the MetS

Clinical measures	WHO (1998)15	EGIR (1999)16	ATPIII (2001)17	AACE (2003)18	IDF (2005)19
Insulin resistance	IGT, IFG, T2DM, or lowered insulin Sensitivity* plus any 2 of the following	Plasma insulin >75th percentile plus any 2 of the following	None, but any 3 of the following 5 features	IGT or IFG plus any of the following based on the clinical judgment	None
Body weight	Wait-hip ratio: Men: >0.90; Women: >0.85 and/or BMI > 30 kg/m2	Waist circumference: Men: ≥94 cm Women: ≥80 cm	Waist circumference: Men: ≥102 cm Women: ≥88 cm	BMI ≥ 25 kg/m2	Increased WC (population specific) plus any 2 of the following
Lipids	TGs ≥150 mg/dL and/ or HDL-C: Men: <35 mg/dL Women: <39 mg/dL	TGs ≥150 mg/dL and/or HDL-C <39 mg/dL in men or women	TGs ≥150 mg/dL HDL-C <40 mg/dL in men or <50 mg/dL in women	TGs ≥150 mg/dL and HDL-C <40 mg/dL in men or <50 mg/dL in women	TGs ≥150 mg/dL or on TGs Rx. HDL-C <40 mg/dL in men or <50 mg/dL in women or on HDL-C Rx
Blood pressure	≥140/90 mm Hg	≥140/90 mm Hg or on hypertension Rx	≥130/85 mm Hg	≥130/85 mm Hg	≥130 mm Hg systolic or ≥85 mm Hg diastolic or on hypertension Rx
Glucose	IGT, IFG, or T2DM	IGT or IFG (but not diabetes)	>110 mg/dL (includes diabetes)	IGT or IFG (but not diabetes)	≥100 mg/dL (includes diabetes)**
Other	Microalbuminuria: Urinary excretion rate of >20 mg/min or albumin: creatinine ratio of >30 mg/g			Other features of insulin resistance***	

1. **Dr. Quazi Audry Arafat Rahman**, MBBS, Assistant Registrar of Medicine, Armed Forces Medical College (AFMC), Dhaka (*E-mail:* audryrahman@gmail.com) 2. **Brig Gen Md. Abdur Razzak**, MBBS, MCPS, FCPS, APLAR Fellow in Rheumatology, Professor and Head, Department of Medicine, AFMC, Dhaka 3. **Lt Col Md Abdul Wahab**, MBBS, MD, Associate Professor of Biochemistry, AFMC, Dhaka.

Note: BMI: body mass index; HDL-C: high density lipoprotein cholesterol; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; Rx: receiving treatment; TGs: triglycerides; T2DM: type 2 diabetes mellitus; WC: waist circumference.

* Insulin sensitivity measured under hyperinsulinemic euglycemic conditions, glucose uptake below lowest quartile for background population under investigation.

** In 2003, the American Diabetes Association (ADA) changed the criteria for IFG tolerance from >110 mg/dl to >100 mg/dl [10].

*** Includes family history of type 2 diabetes mellitus, polycystic ovary syndrome, sedentary lifestyle, advancing age, and ethnic groups susceptible to type 2 diabetes mellitus.

Pathophysiology

There is a wide variation in geographic distribution of MetS. Recent 'catch up' in the developing world emphasize the importance of environmental and lifestyle factors such as the consumption of excess calories and lack of physical activity as being major contributors. Visceral adiposity has been demonstrated to be a primary trigger for most of the pathways involved in MetS, thus stressing the importance of a high caloric intake as a major causative factor[20]. Of all the proposed mechanisms, insulin resistance, neurohormonal activation and chronic inflammation appear to be the main players in the initiation, progression and transition of MetS to CVD (Figure-1)[1]. Insulin resistance-mediated increase in circulating free fatty acids (FFAs) is believed to play a pivotal role in the pathogenesis of MetS[1]. The discovery of endocrine and immune properties of adipocytes has provided further mechanistic insights into the development of MetS. Adipokines released from visceral adipose tissue have been shown to be associated with MetS and CVD[21]. Activation of various pro-atherogenic pathways in MetS culminates in a final common pathway of inflammation that eventually leads to clinical manifestations of MetS[1].

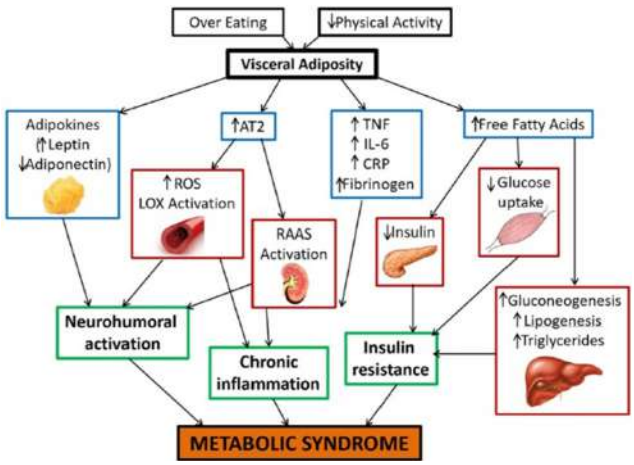

Figure-1: Pathophysiological Mechanisms in Metabolic Syndrome[1]

Associations of Metabolic Syndrome

Abdominal Obesity: The "obesity epidemic" is principally driven by an increased consumption of cheap, calorie-dense food and reduced physical activity. With obesity and progressive adipocytes enlargement, the blood supply to adipocytes may be reduced with consequent hypoxia[22]. Hypoxia has been proposed to be an inciting etiology of necrosis and macrophage infiltration into adipose tissue that leads to an overproduction of biologically active metabolites known as adipocytokines. Adipocytokines integrate the endocrine, autocrine, and paracrine signals to mediate the multiple processes including insulin sensitivity[23], oxidant stress[24], energy metabolism, blood coagulation, and inflammatory responses[25] which are thought to accelerate atherosclerosis, plaque rupture, and atherothrombosis.

Insulin Resistance: Insulin Resistance is defined as a pathophysiological condition in which a normal insulin concentration does not adequately produce a normal insulin response in the peripheral target tissues such as adipose, muscle, and liver. Under this condition, pancreatic beta cell secretes more insulin (i.e., hyperinsulinemia) to overcome the hyperglycemia among insulin-resistant individuals. Although hyperinsulinemia may compensate for insulin resistance to some biological actions of insulin, that is, maintenance of normoglycemia, however, it may cause an overexpression of insulin activity in some normally sensitive tissues. This accentuation of some insulin actions coupled with a resistance to other actions of insulin results in the clinical manifestations of MetS[26]. An inability of the pancreatic beta cells over time to produce sufficient insulin to correct the worsening tissue insulin resistance leads to hyperglycemia and overt T2DM[27].

Dyslipidemia: This dyslipidemia is characterised by a spectrum of qualitative lipid abnormalities reflecting perturbations in the structure, metabolism, and biological activities of both atherogenic lipoproteins and antiatherogenic HDL-C which includes an elevation of lipoproteins containing apolipoprotein B (apoB), elevated TGs, increased levels of small particles of LDL, and low levels of HDL-C. Insulin resistance leads to an atherogenic dyslipidemia in several ways. These anomalies are closely associated with an increased oxidative stress and an endothelial dysfunction, thereby reinforcing the proinflammatory nature of macrovascular atherosclerotic disease[28].

Hypertension: Essential hypertension is frequently associated with the several metabolic abnormalities, of which obesity, glucose intolerance, and dyslipidemia are the most common[29].

Hypercoagulable State: A proinflammatory state is characterized by elevated circulating cytokines and acute-phase reactants (e.g., CRP). Further, a prothrombotic state signifies anomalies in the procoagulant factors, that is, an increase in fibrinogen, factor VII and factor VIII as well as the antifibrinolytic factor (PAI-1), platelet abrasions, and endothelial dysfunctions[28].

Systemic Effects of Metabolic Syndrome

The key sign of metabolic syndrome is central obesity, also known as visceral, male-pattern or apple-shaped adiposity. It is characterized by adipose tissue accumulation predominantly around the waist and trunk.[5] Other signs of metabolic syndrome include high blood pressure, decreased fasting serum HDL cholesterol, elevated fasting serum triglyceride level, impaired fasting glucose, insulin resistance, or prediabetes. Associated conditions include hyperuricemia; fatty liver (especially in concurrent obesity) progressing to nonalcoholic fatty liver disease; polycystic ovarian syndrome in women and erectile dysfunction in men; and acanthosis nigricans (Table II)[28]. MetS is also closely related to several disaeases such as IHD, CVD/Stroke, Obstructive Sleep Apnea, Obesity Hyperventilation Syndrome, Gout, Psoriasis, Subfertility, Depression and various cancers (Figure-2).

Table-II: Systemic effects of MetS.

Renal	Microalbuminuria, hypofiltration, hyperfiltration, glomerulomegaly, focal segmental glomerulosclerosis, and chronic kidney disease[30].
Hepatic	Increased serum transaminase, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), hepatic fibrosis and cirrhosis[31].
Skin	Acanthosis nigricans, lichen planus, systemic lupus erythematosus, burn-induced insulin resistance, psoriasis, androgenetic alopecia, skin tags, skin cancer and acne inversa[32].
Ocular	Nondiabetic retinopathy, age related cataract-nuclear, cortical, posterior subcapsular; central retinal artery occlusion, primary open angle glaucoma, oculomotor nerve palsy and lower lid entropion[33].
Sleep	Obstructive sleep apnea (OSA)[34].
Reproductive system	Hypogonadism, polycystic ovarian syndrome (PCOS) and erectile dysfunction[35].
Cardiovascular system	Coronary heart disease (CHD), myocardial infarction (MI) and stroke[36].
Cancers	Breast, pancreas and prostrate[37].

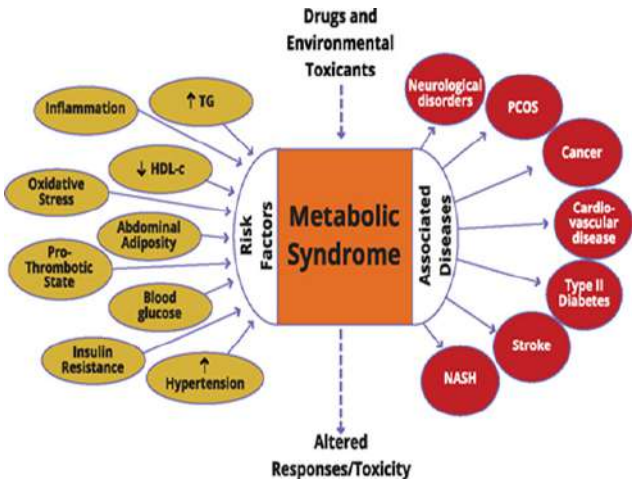

Figure-2: Metabolic Syndrome with its associated risk factors and diseases[38]

Management

MetS is a state of chronic low-grade inflammation with profound systemic effects. Clinical identification and management of patients with MetS are important to begin efforts to adequately implement the treatments to reduce their risk of subsequent diseases[39]. Effective preventive approaches include lifestyle changes, primarily weight loss, diet, and exercise, and the treatment comprises the appropriate use of pharmacological agents to reduce the specific risk factors. Pharmacological treatment should be considered for those whose risk factors are not adequately reduced with the preventive measures and lifestyle changes[40]. Most physicians treat each component of MetS separately, laying a particular emphasis on those components that are easily amenable to the drug treatment. The goals of therapy are to reduce both a short-term and lifetime risk. The presence of the MetS per se indicates a higher lifetime risk. Lifestyle modification treatment should be delivered by a multidisciplinary approach and a team composed of physicians and nonphysician health professionals, such as dieticians or professionals with a master degree in exercise physiology, behavioural psychology, or health education[41].

Weight Reduction: Four therapies can be used for weight reduction: calorie restriction (e.g., 500 kcal/d deficit), increased physical activity, behavioural modification, and, in appropriate patients, FDA-approved weight-reducing drugs[42]. The effective and healthful methods for the long-term weight loss are reduced-energy diets, consisting of a modest 500 to 1000 calories/day reduction[28]. Current physical activity guidelines recommend practical, regular, and moderate regimens for exercise[43]. The standard exercise recommendation is a daily minimum of 30 minutes of moderate-intensity physical activity. However, a preference is given to 60 minutes of moderate-intensity brisk walking to be supplemented by other activities[44]. The emphasis in behavioural change should include the benefit of social support, stress management, the value of a regular exercise regimen, and an improvement in eating habits. The National Institutes of Health guidelines for the treatment of obesity recommend a consideration of pharmaceutical therapy for weight loss for the individuals with a BMI of at least 30 kg/m^2 or for those with a BMI of at least 27 kg/m^2 and comorbidities associated with their excess weight. Pharmacological approaches to weight loss include two main classes: appetite suppressants and inhibitors of nutrient absorption. A single agent is generally recommended and an average weight loss ranges greatly from 5% to 10% of initial weight[45]. Appetite suppressants include phentermine derivatives and sibutramine. Orlistat (an inhibitor of gastrointestinal lipase) is the only nutrient absorption inhibitor currently available. It prevents absorption of up to 30% of the fat consumed and must be taken at the time of consumption[28]. Surgery is recommended for the individuals who do not respond to weight loss diet or medications, are extremely obese (BMI > 40 kg/m^2), or if they have a BMI > 35 to 40 kg/m^2 and one or more

comorbid conditions[45]. Improvements in the metabolic profile have been documented presumably due to the redistribution of adiposity[46]. Bariatric surgery techniques using laparoscopic adjustable banding of stomach along with Roux-en-Y and other forms of gastric bypass are now favoured for the severe and morbid obesity[47].

Dyslipidemia: The guidelines recommend that the LDL-C goals should be set at less than 130 mg/dL with the option of targeting less than 100 mg/dL in the moderately high-risk individuals. Target goals should be set at an LDL-C less than 100 mg/dL in the high-risk patients with the option of aiming for less than 70 mg/dL in the "very high-risk" patient[48]. The goal for the non-HDL-C is 30 mg/dL greater than LDL-C. Statins are considered to be the most effective class of drugs for reducing the LDL-C concentrations due to their minimal drug-drug interactions and side effects[49]. Niacin has favourable effects on essentially all of the abnormalities of the metabolic dyslipidemia. It is considered the most effective agent for raising HDL-C (15 to 35%) and increasing HDL particle size[50]. Niacin significantly lowers TGs (20 to 50%) and LDL-C (5–25%)[49]. The two fibrates currently used clinically are gemfibrozil and fenofibrate, both of which can lower TGs by 25% to 30% with the greater reductions in individuals that are hypertriglyceridemic. Fibrates further increases HDL-C by 5–15% and reduces LDL-C by 0–30%[51].

Hypertension: It has been proposed that angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) should be the first-line classes of agents in the MetS, especially in the setting of diabetes or CKD[52].

Insulin Resistance and Hyperglycemia: In MetS, patients with IFG (or IGT if assessed), weight reduction, increased physical activity, or both will delay (or prevent) the onset of T2DM[53]. In addition, metformin[53], thiazolidinediones[54], and acarbose[55] will lower the risk of T2DM in people with IFG or IGT.

Hypercoagulable State: Measurement of CRP is the most practical way to assess the presence of an inflammatory state. An elevated CRP (≥3 mg/L) is an emerging risk factor for CVD[49]. Several drugs used to treat the other metabolic risk factors have been reported to reduce the CRP levels (e.g., statins, nicotinic acid, fibrates, ACE inhibitors, and thiazolidinediones)[56].

Nutraceuticals in the management of MetS: Dietary supplements that provide health benefits in addition to basic nutritional value are termed nutraceuticals. Various natural compounds derived from plant extracts, spices, herbs and essential oils (Turmeric, Garlic, Cinnamon, Neem, Cumin, Ginger, Grapes, Onions etc) have demonstrable benefit in the management of patients with MetS[1].

Conclusion

MetS is a global epidemic and an established risk factor for atherosclerotic and nonatherosclerotic CVD. Significant variations exist in the diagnostic criteria and definition of MetS, which represent a temporal change in the understanding of this disease. Various stimuli culminating in a state of chronic inflammation seem to be the main pathophysiological drivers for MetS. Existing therapies to tackle various components of MetS are limited by various factors. Firstly, the existence of only a handful of medications that have been shown to have a convincing effect on long-term outcomes makes the choice of therapy challenging. Secondly, the chronic nature of the components of MetS warrant prolonged and often indefinite use of various medications such as statins, leading to an increased burden of drug-related adverse effects and patient noncompliance. In this context, the development of nutraceuticals that are readily available and with minimal side effects may represent an area of promise in the development of novel therapies.

References

1. Yogita Rochlani, Naga Venkata Pothineni, Swathi Kovelamudi, and Jawahar L. Mehta: Metabolic syndrome: Pathophysiology, management and modulation by natural compounds. Ther Adv Cardiovasc Dis 2017; 11(8):215–25.

2. Grundy SM, Cleeman JI, Daniels SR et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Circulation 2005; 112(17):2735–52.

3. Wilson PWF, D'Agostino RB, Parise H et al. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation 2005; 112(20):3066–72.

4. Grundy SM, Hansen B, Smith SC et al. American Heart Association, National Heart, Lung, and Blood Institute, American Diabetes Association. Clinical management of metabolic syndrome: report of the American Heart Association/National Heart, Lung, and Blood Institute/ American Diabetes Association conference on scientific issues related to management. Arterioscler Thromb Vasc Biol 2004; 24(2):e19–e24.

5. Desroches S, Lamarche B. The evolving definitions and increasing prevalence of the metabolic syndrome. Applied Physiology, Nutrition and Metabolism 2007; 32(1):23–32.

6. Kolovou GD, Anagnostopoulou KK, Salpea KD et al. The prevalence of metabolic syndrome in various populations. The American Journal of the Medical Sciences 2007; 333(6):362–71.

7. International Diabetes Federation: The IDF consensus worldwide definition of the metabolic syndrome,http://www.idf.org/metabolic-syndrome.

8. Cameron AJ, Shaw JE, Zimmet PZ. The metabolic syndrome: prevalence in worldwide populations. Endocrinology and Metabolism Clinics of North America 2004; 33(2):351–75.

9. Ponholzer A, Temml C, Rauchenwald M et al. Is the metabolic syndrome a risk factor for female sexual dysfunction in sexually

active women? International Journal of Impotence Research 2008; 20(1):100–4.

10. Wilson PWF, Kannel WB, Silbershatz H et al. Clustering of metabolic factors and coronary heart disease. Archives of Internal Medicine 1999; 159(10):1104–9.

11. Palaniappan L, Carnethon MR, Wang Y et al. Predictors of the incident metabolic syndrome in adults: The Insulin Resistance Atherosclerosis Study. Diabetes Care 2004; 27(3):788-93.

12. Alberti KGMM, Eckel RH, Grundy SM et al. Harmonizing the metabolic syndrome: A joint interim statement of the international diabetes federation task force on epidemiology and prevention; National heart, lung, and blood institute; American heart association; World heart federation; International atherosclerosis society; And international association for the study of obesity. Circulation 2009; 120(16):1640–5.

13. Alberti KGMM, Zimmet P et al. The metabolic syndrome: A new worldwide definition. The Lancet 2005; 366(9491):1059–62.

14. Olijhoek JK, Van Der Graaf Y, Banga J-D et al. The Metabolic Syndrome is associated with advanced vascular damage in patients with coronary heart disease, stroke, peripheral arterial disease or abdominal aortic aneurysm. European Heart Journal 2004; 25(4):342–8.

15. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabetic Medicine 1998; 15(7):539–53.

16. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation: European Group for the Study of Insulin Resistance (EGIR). Diabetic Medicine 1999; 16(5):442–3.

17. Cleeman JI. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). Journal of the American Medical Association 2001; 285(19):2486–97.

18. Einhorn D, Reaven GM, Cobin RH et al. American College of Endocrinology position statement on the insulin resistance syndrome. Endocrine Practice 2003; 9(3):237–52.

19. International Diabetes Federation: The IDF consensus worldwide definition of the metabolic syndrome,http://www.idf.org/metabolic-syndrome.

20. Matsuzawa Y, Funahashi T, Nakamura T. The concept of metabolic syndrome: Contribution of visceral fat accumulation and its molecular mechanism. J Atheroscler Thromb 2011; 18(8):629–39.

21. Wallace AM, McMahon AD, Packard CJ et al. On behalf of the WOSCOPS Executive Committee. Plasma leptin and the risk of cardiovascular disease in the west of Scotland coronary prevention study (WOSCOPS). Circulation 2001; 104(25):3052–6.

22. Cinti S, Mitchell G, Barbatelli G, et al. Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. Journal of Lipid Research 2005; 46(11):2347–55.

23. Saleem U, Khaleghi M, Morgenthaler NG et al. Plasma carboxy-terminal provasopressin (copeptin): A novel marker of insulin resistance and metabolic syndrome. Journal of Clinical Endocrinology and Metabolism 2009; 94(7):2558–64.

24. Tsimikas S, Willeit J, Knoflach M et al. Lipoprotein-associated phospholipase A2 activity, ferritin levels, metabolic syndrome, and 10-year cardiovascular and non-cardiovascular mortality: Results from the Bruneck study. European Heart Journal 2009; 30(1):107–15.

25. Jacobs M, Van Greevenbroek MMJ, Van Der Kallen CJH et al. Low-grade inflammation can partly explain the association between the metabolic syndrome and either coronary artery disease or severity of peripheral arterial disease: the CODAM study. European Journal of Clinical Investigation 2009; 39(6):437–44.

26. Gill H, Mugo M, Whaley-Connell A et al. The key role of insulin resistance in the cardiometabolic syndrome. The American Journal of the Medical Sciences 2005; 330(6):290–4.

27. 82. Petersen KF, Shulman GI. Etiology of insulin resistance. The American Journal of Medicine 2006; 119(5):S10–S16.

28. Jaspinder Kaur: A Comprehensive Review on Metabolic Syndrome; Cardiol Res Pract 2014; 2014:943162

29. Ferrannini E, Natali A. Essential hypertension, metabolic disorders, and insulin resistance. The American Heart Journal 1991; 121(4):1274–82.

30. Locatelli F, Pozzoni P, Del Vecchio L. Renal manifestations in the metabolic syndrome. Journal of the American Society of Nephrology 2006; 17(4, supplement 2):S81–S85.

31. Bruce KD, Byrne CD. The metabolic syndrome: common origins of a multifactorial disorder. Postgraduate Medical Journal 2009; 85(1009):614–21.

32. Padhi T, Garima Metabolic syndrome and skin: psoriasis and beyond. Indian Journal of Dermatology 2013; 58(3):299–305.

33. Chopra R, Chander A, Jacob JJ. Ocular associations of metabolic syndrome. Indian Journal of Endocrinology and Metabolism 2012; 16(supplement 1):S6–S11.

34. Lam JCM, Mary SMI. Sleep & the metabolic syndrome. Indian Journal of Medical Research 2010; 131(2):206–16.

35. Dokras A, Bochner M, Hollinrake E et al. Screening women with polycystic ovary syndrome for metabolic syndrome. Obstetrics and Gynecology 2005; 106(1):131–7.

36. Standl E. Aetiology and consequences of the metabolic syndrome. European Heart Journal, Supplement 2005; 7(supplement D):D10–D13.

37. Handelsman Y. Metabolic syndrome pathophysiology and clinical presentation. Toxicologic Pathology 2009; 37(1):18–20.

38. Mendrick DL, Diehl AM, Lisa S Topor LS et al. Metabolic Syndrome and Associated Diseases: From the Bench to the Clinic. Toxicol Sci 2018; 162(1):36–42.

39. Wong ND. Intensified screening and treatment of the metabolic syndrome for cardiovascular risk reduction. Preventive Cardiology 2005; 8(1):47–54.

40. Deen D. Metabolic syndrome: Time for action. The American Family Physician 2004; 69(12):2875–87.

41. Bellentani S, Grave RD, Suppini A et al. Behavior therapy for nonalcoholic fatty liver disease: The need for a multidisciplinary approach. Hepatology 2008; 47(2):746–54.

42. Donato KA. Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. Archives of Internal Medicine 1998; 158(17):1855–67.

43. Thompson PD, Buchner D, Piña IL et al. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: A statement from the council on clinical cardiology (subcommittee on exercise, rehabilitation, and prevention) and the council on nutrition, physical activity and metabolism (subcommittee on physical activity) Circulation 2003; 107(24):3109–16.

44. Grundy SM, Hansen B, Smith SC et al. American Heart Association; National Heart, Lung, and Blood Institute; American Diabetes Association. Clinical management of metabolic syndrome: report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association conference on scientific issues related to management. Circulation 2004; 109(4):551–6.

45. Wilson PWF, Grundy SM. The metabolic syndrome practical guide to origins and treatment: part I. Circulation 2003; 108(12):1422–4.

46. Folli F, Pontiroli AE, Schwesinger WH. Metabolic aspects of bariatric surgery. Medical Clinics of North America 2007; 91(3): 393–414.

47. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. The Lancet 2005; 365(9468):1415–28.

48. Grundy SM, Cleeman JI, Bairey Merz CN et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004; 110(2):227–39.

49. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult treatment panel III) final report. Circulation 2002; 106(25):3143–421.

50. Kashyap ML, McGovern ME, Berra K et al. Long-term safety and efficacy of a once-daily niacin/lovastatin formulation for patients with dyslipidemia. The American Journal of Cardiology 2002; 89(6):672–8.

51. Leaf DA, Connor WE, Illingworth DR et al. The hypolipidemic effects of gemfibrozil in type V hyperlipidemia. A double-blind, crossover study. Journal of the American Medical Association 1989; 262(22):3154–60.

52. Israili ZH, Lyoussi B, Hernández-Hernández R et al. Metabolic syndrome: Treatment of hypertensive patients. The American Journal of Therapeutics 2007; 14(4):386–402.

53. Knowler WC, Barrett-Connor E, Fowler SE et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. The New England Journal of Medicine 2002; 346(6):393–403.

54. Knowler WC, Hamman RF, Edelstein SL et al. Prevention of type 2 diabetes with troglitazone in the Diabetes Prevention Program. Diabetes 2005; 54(4):1150–6.

55. Chiasson J-L, Josse RG, Gomis R et al. Acarbose for prevention of type 2 diabetes mellitus: The STOP-NIDDM randomised trial. The Lancet 2002; 359(9323):2072–7.

56. Schieffer B, Bünte C, Witte J et al. Comparative effects of AT1-antagonism and angiotensin-converting enzyme inhibition on markers of inflammation and platelet aggregation in patients with coronary artery disease. Journal of the American College of Cardiology 2004; 44(2):362–8.