Metabolic syndrome, cardiovascular disease and type - 2 diabetes

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Abstract

The Metabolic Syndrome, a highly prevalent entity is a clustering of risk factors of metabolic origin that are accompanied by increased risks of cardiovascular disease and type - 2 Diabetes Mellitus. These risk factors are atherogenic dyslipidaemia, elevated blood pressure, raised plasma glucose, a prothrombotic and a proinflammatory states. Two major underlying risk factors for the metabolic syndrome are obesity and Insulin resistance; exacerbated by physical inactivity, advancing age, endocrinal and genetic factors. The condition is progressive and in many patients eventually culminates in type - 2 Diabetes, which further enhances the risk of cardiovascular disease.

Primary treatment for the metabolic syndrome is life style therapy i.e. weight loss, increased physical activity and antiatherogenic diet. As the condition progresses, drug therapies may be required to ameliorate the individual risk factors. Ultimately, it may be possible to develop drugs that will simultaneously modify all the risk factors. However, they are under development and so far have not reached the level of clinical practice.

Introduction

The National Cholestrol Education Program (NCEP) Adult Treatment Panel - III (ATP - III), in 2001 introduced the metabolic syndrome as a risk partner to elevated Low-Density- Lipoproteins (LDL) in cholesterol guidelines[1] in response to the increasing prevalence of obesity and it's metabolic consequences in the USA. The term metabolic syndrome (MS) was applied to the constellation of risk factors that often accompany obesity and are associated with increased risks for both Atherosclerotic Cardiovascular Disease (ASCVD) and type-2 diabetes. The advantage of identifying this particular cluster of risk factors is that it should bring together the fields of cardiovascular disease and diabetes mellitus for a concerted and unified effort to reduce the risk for both conditions simultaneously. Moreover, cardiovascular disease is the foremost killer of patients with diabetes and this is of interest to both fields.[2]

Nomenclature and concept of metabolic syndrome (MS)

The understanding of metabolic syndrome stems from epidemiological studies meant for cardiovascular disease and type-2 diabetes mellitus. The naming of risk factor grouping as syndrome largely came from the diabetes field.[3] Reaven coined the term "Syndrome X" to the constellation of risk factors associated with Insulin resistance[4], which as he contends is the dominant underlying risk factor for the syndrome. In accord, other diabetologists have conferred the name Insulin resistance syndrome.[5]

Obesity has been viewed as an exacerbating factor. Among the diabetologists, some have used the term metabolic syndrome as a more generic name for the collection of metabolic risk factors.[6-7] Epidemiological studies have established a strong association of obesity with ASCVD[8] and type-2 diabetes. Obesity induced risk factors called the metabolic complications of obesity (i.e. plasma cholesterol, elevated blood pressure and diabetes) are strongly related with increased incidence of cardiovacular[9] disease. The ATP III guidelines[1] followed suit and employed the name "Metabolic Syndrome (MS)" because it seemed to be widely used to describe risk-factor aggregation. The syndrome has been assigned international classification of disease (ICD-9) code 277.7) as the dysmetabolic syndrome.[5]

Pathophysiology

The risk factors of MS are of metabolic origin and comprise of atherogenic dyslipidemia, elevated blood pressure, glucose intolerance, a prothrombotic and proinflammatory states.[1,10,11] Atherogenic dyslipidemia includes elevation of lipoproteins containing apolipoprotein B, elevated triglycerides, increased small particles of LDL and low levels of high density lipoproteins (HDL). Elevated plasma glucose falls in the range of either prediabetes or diabetes. A prothrombotic state signifies anomalies in procoagulant factors i.e. an increase in fibrinogen and factor VII as well as antifibrinolytic factor (plasminogen activator inhibitor), platelet abrasions and endothelial dysfunction. A proinflammatory state is characterized by elevated circulating cytokines and acute phase reactants (e.g. C. reactive protein).

The pathogenesis of MS is multifactorial.[1,10,11] The major underlying causes are obesity and Insulin resistance. Obesity is best identified by increased waist circumference (abdominal obesity). Insulin resistance can be secondary to obesity but it can have genetic components. Several other factors exacerbate the syndrome: physical inactivity, advancing age, endocrinal dysfunction and genetic aberrations affecting individual risk factors. The increasing prevalence of metabolic syndrome worldwide seems largely to be due to obesity exacerbated by sedentary lifestyle.[12] Insulin resistance, which is the key phase of metabolic syndrome follows deactivation of Nuclear perioxisome proliferator activated receptors (PPAR) mainly because of obesity.[13] There are two principal pathways of the development of Metabolic Syndrome:-

a. The B-cells of pancreas are preserved resulting in insulin hypersecretion to compensate for insulin resistance. This mainly leads to the macrovascular complications of MS.[13,14]

b. Massive damage to B cells of pancreas leading to reduced insulin secretion and hyperglycaemia. This pathway leads to both microvascular and macrovascular complications.

It is suggested that PPAR based appraisal of metabolic syndrome and type-2 diabetes mellitus may improve the understanding of these diseases and may set basis for a comprehensive approach to their treatment.[14]

The factor that dominates in obesity is the permanent elevation of plasma free fatty acid (FFA) and predominant utilization of lipids by the muscles inducing a diminution of glucose uptake and insulin resistance. People who develop type-2 Diabetes pass through the phases of excessive adipogenesis (obesity), whereas PPAR modulation, insulin resistance, hyperinsulinemia, pancreatic B cell stress and damage leads to progressive decrease of insulin secretion and impaired post parandial and fasting glucose.[15,16]

Further more, adipose tissue plays an important role in whole - body energy homeostasis both in terms of fat storage and release as well as through the effects of adipocyte cytokines.[5] Leptin deficiency is associated with hyperphagia, lack of satiety and also increased body fat.[17] Infusion of insulin and glucose in humans to maintain euglycaemia increases leptin levels after 3 hours and decreases level of adiponectin.[18] Adiponection has insulin sensitizing action, anti-inflammatory effects on vascular endothelium and increases HDL-cholesterol.[19] Its levels increase with weight loss and thiazolidinediones. Thus there are acquired as well as genetic causes of metabolic syndrome and the discovery of nuclear PPARS have further improved the understanding of the pathogenesis of this condition.

Clinical Outcome and Natural History

The relative risk of atherosclerotic cardio-vascular disease (ASCVD) ranges from 1.5 to 3.0 among patients with MS depending upon the stage of progression.[20] When diabetes is not yet present, risk of progression to type-2 diabetes is about five fold than compared with those who

don't have MS.[21] Once diabetes has developed, cardiovascular risks increase even more.

Most individuals who develop the syndrome first acquire abdominal obesity without risk factors. But with the passage of time, multiple risk factors begin to emerge. Initially these are elevated to a small extent, but later in many individuals they are categorically raised.[22] In some, syndrome culminates in type-2 diabetes with all its consequent complications. If ASCVD develops complications like cardiac arrhythmias, and heart failure, then thrombotic episodes ensue. When ASCVD and diabetes coexist, the risk of subsequent cardiovascular morbidity and mortality is very high. The syndrome runs a progressive course with advancing age causing worsening of obesity and physical inactivity.

Patients with MS can manifest a variety of other conditions such as fatty liver, gallstones, sleep apnea and gout. Presence of several or all of these outcomes leads to the use of multiple medicines (polypharmacy) which carry the risk of drug interactions, interfere with compliance and imposes a prohibiting cost burden.[21,22]

Diagnosis and Risk Assessment

In 1998, a diabetes working group of the World Health Organization (WHO) proposed a set of criteria for a clinical diagnosis of the metabolic syndrome.[6] These include clinical evidence of insulin resistance such as impaired glucose tolerance, impaired fasting glucose or type-2 diabetes as necessary for the diagnosis. Shortly afterward European group for study of Insulin Resistance (EGIR) proposed the same criteria.[23] The ATP III1 simplified the WHO criteria by requiring three of the five simple clinical measures:[1,2,15,16] increased waist circumference, elevated triglycerides, reduced HDL, elevated glucose and elevated blood pressure.

The International Diabetes Federation (IDF) replaced WHO criteria with those closer to ATP III. Waist circumference threshold were made ethnic specific and abdominal obesity was required for diagnosis.[24] Thus the ATP III[10] update and the IDF[11] report harmonize the clinical diagnosis of MS when at least three of the following criteria are present:-

1. Central obesity as defined by ethnicity specific values of waist circumference ≥ 90 cm in men and ≥ 80 cm in women for South Asians and South East Asians.

2. Elevated triglycerides ≥150mg/dl (1.7m mol/L) or specific treatment for lipid abnormality.

3. Reduced HDL cholestrol < 40 mg/dL in men and < 50 mg/dL in women.

4. High blood pressure ≥130/85 mm Hg or treatment of previously diagnosed hypertension.

5. High fasting blood glucose (FPG) ≥ 100mg/dL and <120 mg/dl or previously diagnosed type 2 diabetes.

Importantly, the MS is not a reliable tool for global risk assessment for ASCVD in short term (i.e. 10 years) as it does not include all risks i.e. age, gender and smoking, total cholesterol etc. All patients with MS deserve global risk assessment whether by risk factor algorithms or by atherosclerosis imaging in-order to identify persons for preventive medications.[25]

Management

Once a person is found to have the syndrome, lifestyle therapy should be introduced, reinforced and monitored. Drug therapy is a secondary consideration that should be guided by global risk assessment.

The ATP III[1] recommended lifestyle therapy that includes weight reduction, increased physical activity and an anti-atherogenic diet. Smoking cessation is mandatory. Over the past century there is an evidence of approximately 15% weight increase among the USA population.[26] A 5% - 10% weight loss is the goal. Weight loss follows low fat diet, exercise for 60-90 minutes per day and regular meals.[27] Carbohydrate restriction will be effective in improving the atherogenic phenotype. Life style intervention unfortunately is often neglected in routine practice.

Drug Therapies

The idea of reducing multiple risk factors with a single drug or a combination is attractive and needed. At present, the only drugs approved for treatment are those that target the individual risk factors. Lipid lowering agents, anti hypertensive and hypoglycaemic drugs, anti platelet and weight loss agents. For the treatment of risk factors of MS, the physician should follow current treatment guideline of the NCEP[1], the sixth joint national commission (JNC-IV) for blood pressure treatment[28], the Amercian Diabetes Association[29], the American Heart Association[10] and the National Institute of Health obesity Initiative.[30]

Pharmacological therapies for the two underlying risk factors for the syndrome i.e. obesity and insulin resistance are under development. They nonetheless hold promise for adding benefit for delaying progression of the condition and to reduce the risk for ASCVD and / or diabetes. The drugs include weight reducing agents, peroxisome proliferator activated receptor (PPAR) alpha agonists (fibrates), PPAR- gamma agonist (Thiazdidinediones [TZDS]), and dual PPAR agonists.

Two weight loss drugs - Sibutramine and orlistat are already FDA approved. They improve all of the metabolic

syndrome risk factors but produce only moderate weight loss.[31,32] A new promising weight loss drug is a selective cannabinoid receptor-1 (CB1) antagonist called Rimonabant. Endocannabinoids activate G-protein coupled CD, in hypothalamus and limbic forebrain, thus accentuating hyperphagia.[33] Rimonabant suppresses endogenous activation of the endocannabinoid system. The drug causes 5% to 10% weight loss up to two years and may have systemic effects to reduce MS risk factors.[33]

Clinical trials show that fibrates independently reduce risk of ASCVD by treating atherogenic dyslipidemia and possibly because of anti-inflammatory properties.[1] TZDS lessen insulin resistance and moderately reduce metabolic risk factors. A recent clinical trial strongly suggests reduction of cardiovascular outcomes with one TZD, pioglitazone.[34] Dual PPAR (combined alpha and gamma) agonists such as Tesaglitazar have favourable effects on several metabolic risk factors.[35] Inspite of promise, all these drugs have outcome hurdles to mount before they can be approved for routine use in patients with MS.

In conclusion, the metabolic syndrome is a cluster of risk factors of metabolic origin that together are associated with higher risk for ASCVD and Type - 2 Diabetes involving approximately one fourth of adults. It is accompanied by Insulin resistance and its increasing prevalence is due to escalating obesity and physical inactivity. The syndrome is a progressive condition that worsens with advancing age and increasing obesity often culminate in type-2 Diabetes mellitus which carries particularly high risk for both cardiovascular events and other complications. However, MS itself is not a robust risk assessment tool for estimating absolute 10 years risk. Primary intervention is lifestyle therapy particularly weight reduction and increased exercise. Drug therapies may help control the various risk factors of MS and thus ASCVD and type-2 Diabetes.

References

1. 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: 3143-421.

2. No authors listed. Diabetes mellitus: a major risk factor for cardiovascular disease. A joint editorial statement by the American Diabetes Association; The National Heart, Lung and Blood Institute; The Juvenile Diabetes Foundation International; The National Institute of Diabetes and Digestive and Kidney Diseases; and the American Heart Association. Circulation 1999; 100: 1132-33.

3. Grundy SM. Metabolic syndrome: connecting and reconciling cardiovascular and diabetes worlds. J Am Coll Cardiol 2006; 47:1093-100.

4. Reaven GM. Role of insulin resistance in human disease (syndrome X): an expanded definition. Annu Rev. Med. 1993; 44: 121-31.

5. Bloom garten ZT. Highlights From the First World Congress on the Insulin

6. 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. Diabet Med 1998; 15: 539-53.

7. Groop L. Genetics of the metabolic syndrome. Br J Nutr 2000; 83 Suppl 1: S39 - 48.

8. Wilson PW, D'Agostino RB. Sullivan L. Parise H. Kannel WB. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. Arch Intern Med 2002; 162: 1867-72.

9. Pi-Sunyer FX. The obesity epidemic: pathophysiology and consequences of obesity. Obes Res 2002; 10 Suppl 2: 97S-104S.

10. Grundy SM, Cleeman JI, Danies SR, Donato KA, Eckel KH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: An American Heart Association/ National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112: 2735-52.

11. Alberti KG, Zimmet P, Shaw J. IDF Epidemioligy Task Foce Consensus Group. The metabolic syndrome a new worldwide difinition. Lancet 2005; 366; 1059-62.

12. Park YW, Zhu S, Palaniappan L, Heshka S, Carnethon MR, Heymsfield SB. The metabolic syndrome: prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988-1994. Arch Intern Med 2003; 163: 427-36.

13. Tenenbaum A, Fisman EZ Motro M. Metabolic syndrome and type 2 diabetes mellitus: focus on peroxisome proliferator activated receptors (PPAR). Cardiovascular Diabetology 2003; 2:4.

14. Berger J, Moller DE. The mechanisms of action of PPARs. Annu Rev Med 2002, 53: 409-35.

15. Hayden MR, Tyagi SC. Intimal redox stress: Accelerated atherosclerosis in metabolic syndrome and type 2 diabetes mellitus. Atheroscleropathy. Cardiovase Diabetol 2002; 1:3.

16. Porte D Jr, Kahn SE. Beta-cell dysfunction and failure in type 2 diabetes: potential mechanisms. Diabetes 2001, 50(Suppl 1): S160-163.

17. Farooqi IS, Keogh JM, Kamath S, Jones S, Gibson WT, Trussel R et al. Partial leptin deficiency and human adiposity. Nature 2001; 414: 34 - 5.

18. Saad MF, Khan A, Sharma A, Michael R, Riad-Gabriel MG, Boyadjian R et al. Physiological insulinemia acutely modulates plasma leptin. Diabetes 1998; 47: 544-9.

19. Cnop M, Havel PJ, Utzschneider KM, Carr DB, Sinha MK, Boyko EJ et al. Ralationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins; evidence for independent roles of age and sex. Diabetologia 2003; 46: 459-69.

20. McNeill AM, Rosamond WD, Girman CJ, Golden SH, Schmidt MI, East HE et al. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the arteriosclerosis risk in communities study. Diabetes Care 2005; 28: 385-90.

21. Schmidt Ml, Duncan BB, Bang H, Pankow JS, Ballantyne CM, Golden SH et al. Identifying individuals at high risk for diabetes: The Atherosclerosis Risk in Communities study. Diabetes Care 2005; 28: 2013-18.

22. Meigs JB, Nathan DM, Wilson PW, Cupples LA, Singer DE. Metabolic risk factors worsen continuously across the spectrum of nondiabetic glucose tolerance. The Framingharm Offspring Study. Ann Intern Med 1998; 128: 524-33.

23. Balkau B. Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). Diabet Med 1999; 16: 442-3.

24. Alberti KG, Zimmet P, Shaw J, IDF Epidemiology Task Force Consensus Group. The metabolic syndrome-a new worldwide definition. Lancet 2005; 366: 1059-62.

25. Grundy SM. Atherosclerosis imaging for risk assessment and primary prevention of cardiovascular disease. Prog Cardiovasc Dis 2003; 46:115-21.

26. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. JAMA. 2002; 288: 1723-7.

27. Wyatt HR, Grunwald GK, Mosca CL, Klem ML, Wing RR, Hill JO. Long-term weight loss and breakfast in subjects in the Naitonal Weight Control Registry. Obes Res 2002; 10: 78-82.

28. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al., for the National Heart, Lung, and Blood Institute Joint National

Resistance Syndrome 2003;21-22, Los Angeles, California. Medscape Diabetes and Endocrinology 2004; 6.

Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003; 289: 2560-72.

29. No authors listed. American Diabetes Association. Clinical practice recommendations 2005. Diabetes Care 2005; 28(Suppl 1): S1-79.

30. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. The Evidence Report. National Institutes of Health. Obes Res 1998; 6 Suppl 2: 51S-209S.

31. Arterburn DE, Crane PK, Veenstra DL. The efficacy and safety of sibutramine for weight loss: a systematic review. Arch Intern Med. 2004; 164: 994-1003.

32. Curran MP, Scott LJ. Orlistat: a review of its use in the management of patients with obesity. Drugs 2004; 64: 2845-64.

33. Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rossner S; R10-Europe Study Group. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. Lancet 2005; 365: 1389-97.

34. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive study (PROspective pioglitAzone Clinical Trial in macro Vascular Events): a randomized controlled trial. Lancet 2005; 366: 1279-89.

35. Fagerberg B, Edwards S, Halmos T, et al. Tesaglitazar, a novel dual peroxisome proliferator-activated receptor alpha/gamma agonist, dose-dependently improves the metabolic abnormalities associated with insulin resistance in a non diabetic populaion. Diabetologia 2005; 48: 1716-25.