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Metabolic Syndrome

Mukund R Mogarekar, Mohit V Rojekar* and Swati D Sawant

Department of Biochemistry, Rajiv Gandhi Medical College, Kalwa, Thane, India

***Corresponding author:** Mohit V Rojekar, Department of Biochemistry, Rajiv Gandhi Medical College, Kalwa, Thane, India, Tel: 918390465676; E-mail: drmohi44@gmail.com

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Abstract

The metabolic syndrome (MetS) is a constellation of interrelated risk factors of metabolic origin - metabolic risk factors - that appear to directly promote the development of atherosclerotic cardiovascular disease (CVDs). It consists of atherogenic dyslipidemia (elevated triglycerides and apolipoprotein B-containing lipoproteins and decreased high-density lipoproteins [HDL]), elevations of blood pressure (BP) and glucose, and prothrombotic and proinflammatory states. The review focuses on epidemiology, pathophysiology of the MetS. Metabolic syndrome is discussed with respect to developmental (childhood and infancy) aspects, genomics and mechanisms of carcinogenesis.

Keywords: Metabolic syndrome; Epidemiology; Pathophysiology; Developmental aspect; Genomics; Carcinogenesis

Background

Many centuries ago 'Charwaka', an Indian philosopher of ancient times, quoted "one should eat oily, spicy things even on credits. Because once you have burnt to ashes or lay down deep in the earth, there will be no coming back." This is one of the several streams of Indian philosophy. Now-a-days as a result of changes in lifestyles and eating habits, the chemistry of human body starts changing. Even if people don't know Charwaka, might be due to various reasons, they have started adapting his principle. Junk foods, lack of exercise, psychosocial stress are the conspicuous ones among the various reasons that are leading to dreadful metabolic disorders. The metabolic syndrome is one of them.

The metabolic syndrome (MetS) is a constellation of interrelated risk factors of metabolic origin - metabolic risk factors - that appear to directly promote the development of atherosclerotic cardiovascular disease (CVDs) [1]. The metabolic syndrome has become one of the most important topics for this decade because of the marked increase in cardiovascular risk associated with a clustering of risk factors.

It consists of atherogenic dyslipidemia (elevated triglycerides and apolipoprotein B-containing lipoproteins and decreased high-density lipoproteins [HDL]), elevations of blood pressure (BP) and glucose, and prothrombotic and proinflammatory states [2]. The constellation of dyslipidemia (hypertriglyceridemia and low levels of high-density lipoprotein cholesterol), elevated blood pressure, impaired glucose tolerance, and central obesity is now classified as metabolic syndrome, also called syndrome X [3].

Several expert groups have attempted to set forth simple diagnostic criteria for use in clinical practice to identify patients who manifest the multiple components of the metabolic syndrome. These criteria have varied somewhat in specific elements, but in general, they include a combination of multiple and metabolic risk factors [3].

The definitions of metabolic syndrome include those proposed by the World Health Organization (WHO), the European Group for the Study of Insulin Resistance (EGIR), the US National Cholesterol Education Program (ATPIII) and International Diabetes Federation (IDF) [4-7].

Comparison of Definitions

In 1998, the WHO criteria for diagnosing the metabolic syndrome put forth. It is based on the insulin resistance in the form of diabetes mellitus or impaired glucose tolerance (IGT). Other criteria are any two of central obesity [Waist hip ratio >0.90 (Male), more than 0.85 (Female) and/or BMI >30 kg/m^2], lipidemia [TG >1.7 mmol/l, HDL-C <0.9 mmol/l (Male), <1.0 mmol/l (Female)], hypertension (>140/90 mm Hg) or microalbuminuria (urinary albumin 20 µg/min or greater, or albumin-to-creatinine ratio 30 mg/g or greater).

Immediately next year in 1999, the European Group for the Study of Insulin Resistance (EGIR) proposed new criteria. Microalbuminuria was excluded. Insulin resistance was defined as insulin level more than 75th percentile of normal non-diabetic subjects. For central obesity, waist circumference was the only criteria. Glycemia assessment (Fasting glucose ≥ 6.1 mmol/l & <7 mmol/) was included. Reference values for lipidemia were modified.

Later in the year 2001, NCEP ATP III came in to being. Three or more of the glycemia, lipidemia, obesity and hypertension were necessary for diagnosis. Only difference made was modified reference waist circumference and blood pressure.

In the year 2005, IDF proposed diagnostic criteria for metabolic syndrome. This was based on Central obesity of more than 30 Kg/m^2 with ethnic specificity plus 2 or more of hyperglycemia, hyperlipidemia and hypertension. Modifications were made in glycemia (more than 100 mg%) and HDL levels. In each of derangements a new assessment criteria of normal levels with treatment was included.

WHO, EGIR, NCEP ATP III were lacking any ethnic specificity, as found in IDF. Also the insulin measurement which is available only

with higher centers is a main drawback for WHO and EGIR criteria. Depending upon hyperglycemia, IDF criteria is more stringent. One can conclude that WHO and EGIR criteria are insulinocentric while the obesity is central to the IDF (Table 1).

Definitions of Metabolic Syndrome

Obesity and physical inactivity are the driving forces behind the syndrome but another set of factors, metabolic susceptibility, usually is required for the MetS to become evident [8] Susceptibility factors include adipose tissue disorders (typically manifest as abdominal obesity), genetic and racial factors, aging, and endocrine disorders [9].

Criteria	WHO	EGIR	NCEP ATP III	IDF
	Glucose intolerance, IGT or diabetes and/or insulin resistance plus 2 or more of the following:	IR or fasting hyperinsulinaemia (highest 25 %) plus 2 or more of the following	3 or more of the following:	Central obesity (>30 Kg/m^2) plus 2 or more of the following
Glycemia		Fasting glucose ≥ 6.1 mmol/l and <7 mmol/l	Fasting glucose ≥ 6.1 mmol/l	Fasting glucose ≥ 5.6 mmol/l Or previously diagnosed Type 2 diabetes
Central obesity	Waist-hip ratio >0.90 (M) >0.85 (F) and/or BMI>30 kg/sqm	Waist ≥ 94 cm (M) ≥ 80 cm (F)	Waist > 102 cm (M) > 88 cm (F)	----
Lipidemia	TAG ≥ 1.7 mmol/l HDL-C<0.9 mmol/l (M)<1.0 mmol/l (F)	TAG>2.0 mmol/l HDL-C<1.0 mmol/l or dyslipidaemia Treatment	TAG ≥ 1.7 mmol/ HDL-C<1.0 mmol/l (M) <1.3 mmol/l (F)	TAG ≥ 1.7 mmol/l or specific treatment HDL-C <1.03 mmol/l (M) <1.29 mmol/l (F)or specific treatment
Blood pressure	>140 / 90 mm Hg	≥ 140 and/or 90 mm Hg or specific treatment	≥ 135 / 85 mm Hg or treatment	SBP ≥ 130 mm Hg DBP ≥ 85 mm Hg or specific treatment
Others	Micro-albuminuria			

Table 1: Three or more of the glycemia, lipidemia, obesity and hypertension were necessary for diagnosis. Only difference made was modified reference waist circumference and blood pressure.

MetS is associated with many diseases. Two primarily clinical outcomes of MetS are CVD and NIDDM, which both are leading diseases in the structure of the morbidity and mortality worldwide. In fact, all individual components of MetS are risk factors for CVD [10,11]. MetS implies even higher risk for coronary heart diseases (CHD) and CVD [12,13] and death from them [14] than individual abnormalities. Indeed, MetS was shown to be the most important factor responsible for myocardial infarction in the population younger than 45 [15]. Similarly, individual components of MetS (obesity, hypertension, low levels of HDL cholesterol, elevated TAG levels, and impaired fasting glucose) and MetS per se are all significant predictors of NIDDM [3,13].

MetS and its single components are tightly connected with the development of non-alcoholic fatty liver disease [16] which is one of the most distributed liver diseases in industrial countries [17]. MetS is more prevalent in patients with polycystic ovarian syndrome (PCOS) [18]. The correlation was found between PCOS and single components of MetS such as insulin resistance and obesity [19]. Linking factor for both syndromes is considered to be insulin resistance [20] Breast cancer is the main cause of death from cancer in women. It was shown, that individual components of MetS increase the risk for breast cancer [21]. MetS is also associated with schizophrenia [22] and sleep apnea syndrome [23]. The MetS is often associated with other medical conditions, notably, fatty liver, cholesterol gallstones, obstructive sleep apnea, gout, depression, musculosketal disease, and polycystic ovarian syndrome [24].

Epidemiology

Depending upon the criteria used, the prevalence varies. Least with initial version of NCEP ATP III, maximum prevalence found to be with IDF criteria. This is because IDF adapted lower cut off for glycemia and waist circumference [25]. Series of studies showed the change in the trend of prevalence of MetS. There is always increasing trend with increasing age. Prevalence of glycemia, hypertension and triglyceridemia shows downward trend which corresponds to the increase in hypolipidemic, antihypertensive and hypolipidemic drugs respectively [26].

Obesity is a major determinant of the MetS. It is estimated that by 2030 the absolute number of obese individuals could rise to a total of

1.12 billion, accounting for 20% of the world's adult population [27]. This will definitely contribute to the increasing global burden of MetS in near future. DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) describes significant increase in death by all causes and cardiovascular complications in individuals with MS [28].

Pathophysiology of Metabolic Syndrome

Insulin resistance and obesity

The most accepted hypothesis to describe the pathophysiology of the metabolic syndrome is insulin resistance. That is why the metabolic syndrome is also known as the insulin resistance syndrome. Insulin resistance has been defined as a defect in insulin action that results in hyperinsulinaemia, necessary to maintain euglycaemia. The predominant underlying risk factors for the syndrome appear to be abdominal obesity and insulin resistance [29-31].

A major contributor to the development of insulin resistance is an overabundance of circulating fatty acids, released from an expanded adipose tissue mass. Free fatty acids (FFAs) reduce insulin sensitivity in muscle by inhibiting insulin-mediated glucose uptake. Increased level of circulating glucose increases pancreatic insulin secretion resulting in hyperinsulinemia. In the liver, FFAs increase the production of glucose, triglycerides and secretion of very low density lipoproteins (VLDL). The consequences of this are the reduction in glucose transformation to glycogen and the increased lipid accumulation in triglycerides (TG) [32]. Insulin is an important antilipolytic hormone. In the case of insulin resistance, the increased amount of lipolysis of stored triacylglycerol molecules in adipose tissue produces more fatty acids, which could further inhibit the antilipolytic effect of insulin, creating additional lipolysis [33].

The adipose tissue of obesity exhibits abnormalities in the production of several adipokines that may separately affect insulin resistance These include increased production of inflammatory cytokines, plasminogen activator inhibitor-1 and other bioactive products; at the same time the potentially protective adipokine, adiponectin are reduced [34-36].

Obesity is involved in the onset of MetS through the alteration of oxidative status of organism. In fact, oxidative stress is tightly involved in the increase of blood pressure through the regulation of a variety of factors [37]. More importantly, it is associated with the development of insulin resistance, another essential component of MetS. In fact, oxidative stress induces insulin resistance in variety of cells which regulate systemic response to insulin: adipocytes, muscle and liver cells [38-40]. It has been proven recently, that oxidative stress has a causative role and is primarily in relation to the onset of insulin resistance [41]. Ultimately, oxidative stress has been shown to correlate with dislipidemia (high triacylglyceride concentration, low level of high-density lipoprotein cholesterol) and abdominal fat [42]. In patients with MetS and thus might be considered as a linking factor between the single components of MetS. A genetic predisposition to defective insulin secretion when combined with insulin resistance can raise plasma glucose to abnormal levels [43]. Pathophysiology and effects of proinflamatory state are shown in Figures 1 and 2.

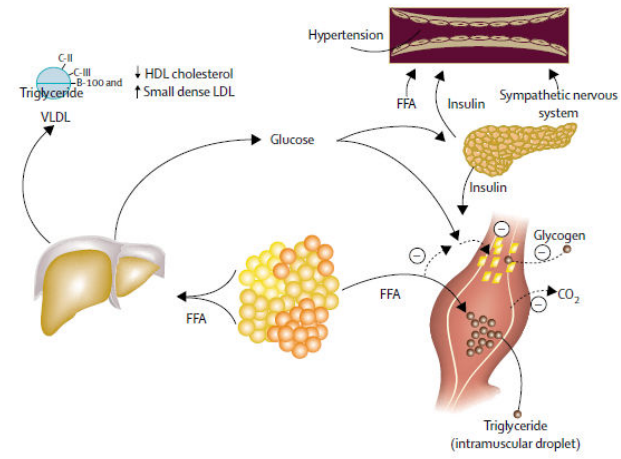

Figure 1: Pathophysiology of metabolic syndrome.

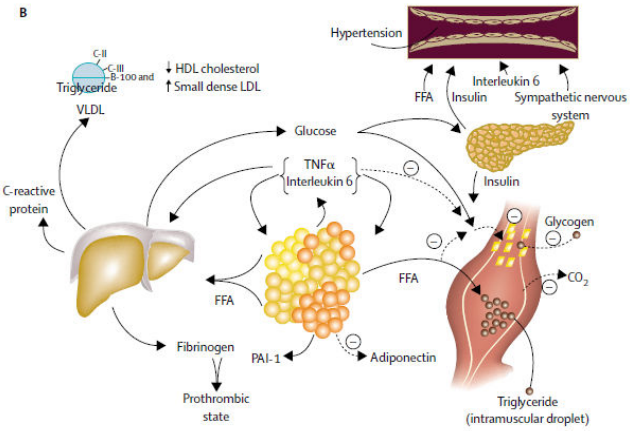

Figure 2: Paracrine and endocrine effects of proinflamatory state.

Free fatty acids (FFA) are released in abundance from an expanded adipose tissue mass. In the liver, FFAs leads to an increased production of glucose, triglycerides and secretion of very low density lipoproteins (VLDL). Associated lipid/lipoprotein abnormalities include reductions in high density lipoprotein (HDL) cholesterol and an increased density of low density lipoproteins (LDL). FFAs also reduce insulin sensitivity in muscle by inhibiting insulin mediated glucose uptake. Increase in circulating glucose and to some extent FFAs increase pancreatic insulin secretion resulting in hyperinsulinemia. This may results in enhanced sodium reabsorption and increased sympathetic nervous system (SNS) activity and contributes to the hypertension as might increase levels of circulating FFAs.

Metabolic Syndrome and Development

IDF tries to classify age related developmental changes. It age groups as 6-10, 10-16 and more than 16 years. There is lack of data available for the age group less than 6 years. Different cutoff values are

assigned to the parameters for children and adolescents. Infants born to the diabetic mother or born to those having gestational diabetes mellitus are more susceptible for the development of MetS. Large for Gestational Age (LGA) babies born to diabetic mothers are more susceptible to development of MetS in childhood [44].

Recent epidemiological and environmental studies suggest relationship between antenatal environment and risk of developing insulin resistance with metabolic syndrome in middle age. This may caused by prenatal and postnatal environmental mismatch. Epigenetically if such changes are passed to further generations, may develop the disease even at low exposure [45].

Metabolic Syndrome and Genomics

Different methods are implemented for genetic studies in MetS. Inheritance patterns are studied using linkage analysis. Traits co-inherited with disease causing mutation are used to detect mutations. The results of genome wide association studies (GWAS) are available where single nucleotide polymorphism (SNPs) is searched to study the disorder. Deviation in expression of gene activity without DNA changes is studied in epigenetic studies. Proteomics is one more tool for genomic analysis of MetS.

Many genes are studied for possible contribution to the development of MetS. They include lipoprotein lipase (LPL), apolipoprotein E (APOE) gene, [46]. Many SNPs are discovered in relation to the hypertension and body mass index [47,48]. Melanocortin receptor 4 (MC4R) gene and fat mass and obesity associated (FTO) gene are the important genes studied well with respect to obesity. Monogenic forms of obesity are related to the MC4R gene though some forms of polygenic obesity are also associated with it [49]. A particular form of SNP in FTO gene is associated with increased hunger, reduced satiety finally to raise BMI. As compared to the normal population, FTO gene is more prevalent in those with MetS [50].

Metabolic Syndrome and Cancer

Metabolic syndrome is associated with various cancers. The risk differs depending upon sex, ethnicity and criteria used for defining MetS. According to some meta-analytical studies, risk ratios for hepatic, colorectal, pancreatic carcinomas are higher in males while that in females prevalent are endometrium, pancreatic and breast cancer. In both males and females, gastric, lung and bladder cancers are rare [51]. Mechanisms for the link between metabolic syndrome and cancer risk are not fully understood.

Metabolic syndrome may be harbinger of cancer risk in future through decreased physical activity, consumption of high dietary fat and energy dense foods, low fiber intake, and damage by oxidative stress [52]. Inflammatory state is produced due to secretion of the inflammatory cytokines by adipocytes and immune cells which is fertile ground for tumors. Cytokines are link between the inflammation and cancer. Loss of function of tumor suppression, increase frequency of cell cycle, increase oncogenic expression are results of cytokines and other mediators of inflammation like tumor necrotic factor (TNF), reactive oxygen species (ROS) [53].

Peroxisome proliferator activated receptors (PPAR) are the receptor involved in glucose metabolism through action over insulin sensitivity and is one of the target diabetes treatment. This is a ligand-activated transcription factor belong to nuclear hormone receptor superfamily. PPARγ interaction with cytokines has key role to play in carcinogenesis [54]. Insulin resistance through insulin like growth factor-1 (IGF1) stimulates carcinogenesis. IGF1 has proliferative and antiapoptotic action over tumors. Important components of carcinogenesis cellular proliferation and angiogenesis are stimulated by IGF1 [55]. Adiponectine which is reduced with increase in adipocyte cell mass has tumor preventive action. In MetS adiponectin secretion is reduced. Antineoplastic activity is by the virtue of anti-proliferative and anti-inflammtory effect with insulin antagonist action [56].

Conclusion

There are various styles for diagnosis of metabolic syndrome depending upon the criteria and cut off values used for them by the authorities. Depending on these styles, prevalence of metabolic syndrome change. Some criteria are modified for different ethnic groups. Some are more stringent as compared to others.

Developmental aspects play important role in metabolic syndrome. Along with environmental factors genetic makeup of person decides expression of MetS. Various tests are there to study the genomics of MetS. Genomic analysis provides information about SNPs or other genetic changes leading to MetS. Metabolic syndrome is not only limited to its components but also some dreadful diseases like cancers found their origin in MetS.

Thus metabolic syndrome is not the single entity but the orchestra of many disorders. Proper knowledge of diagnosing criteria, epidemiology, developmental aspects and genomics can help in timely diagnosis as well as finding the new avenues for treatment.

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: 3143-3421.
2. Grundy SM (2008) Metabolic syndrome pandemic. Arterioscler Thromb Vasc Biol 28: 629-636.
3. Alshehri AM (2010) Metabolic syndrome and cardiovascular risk. J Family Community Med 17: 73-78.
4. Alberti KG, Zimmet PZ (1998) 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 15: 539-553.
5. Balkau B, Charles MA (1999) Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR) Diabet Med 16: 442-443.
6. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. 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) (2001) JAMA 285: 2486-2497.
7. Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group (2005) The metabolic syndrome--a new worldwide definition. Lancet 366: 1059-1062.
8. Grundy SM (2007) Metabolic syndrome: a multiplex cardiovascular risk factor. J Clin Endocrinol Metab 92: 399-404.
9. Park YW, Zhu S, Palaniappan L, Heshka S, Carnethon MR, et al. (2003) 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 163: 427-436.

10. Gerstein HC (1999) Is glucose a continuous risk factor for cardiovascular mortality? Diabetes Care 22: 659-660.
11. Balkau B, Shipley M, Jarrett RJ, Pyörälä K, Pyörälä M, et al. (1998) High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men. 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study. Diabetes Care 21: 360-367.
12. Alexander CM, Landsman PB, Teutsch SM, Haffner SM (2003) Third National Health and Nutrition Examination Survey (NHANES III); National Cholesterol Education Program (NCEP). NCEP - defined metabolic syndrome, diabetes and prevalence of coronary heart disease among NHANES III participants age 50 years and older. Diabetes 52: 1210-1214.
13. Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB (2005) Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation 112: 3066-3072.
14. Gao W; DECODE Study Group (2008) Does the constellation of risk factors with and without abdominal adiposity associate with different cardiovascular mortality risk? Int J Obes (Lond) 32: 757-762.
15. Marchesini G, Brizi M, Morselli-Labate AM, Bianchi G, Bugianesi E, et al. (1999) Association of nonalcoholic fatty liver disease with insulin resistance. Am J Med 107: 450-455.
16. Knobler H, Schattner A, Zhornicki T, Malnick SD, Keter D, et al. (1999) Fatty liver--an additional and treatable feature of the insulin resistance syndrome. QJM 92: 73-79.
17. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, et al. (2004) Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology 40: 1387-1395.
18. Cheung LP, Ma RC, Lam PM, Lok IH, Haines CJ, et al. (2008) Cardiovascular risks and metabolic syndrome in Hong Kong Chinese women with polycystic ovary syndrome. Hum Reprod 23: 1431-1438.
19. Dunaif A (1997) Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev 18: 774-800.
20. Martínez-Bermejo E, Luque-Ramírez M, Escobar-Morreale HF (2007) Obesity and the polycystic ovary syndrome. Minerva Endocrinol 32: 129-140.
21. Muti P, Quattrin T, Grant BJ, Krogh V, Micheli A, et al. (2002) Fasting glucose is a risk factor for breast cancer: a prospective study. Cancer Epidemiol Biomarkers Prev 11: 1361-1368.
22. Ryan MC, Thakore JH (2002) Physical consequences of schizophrenia and its treatment: the metabolic syndrome. Life Sci 71: 239-257.
23. Hansel B, Cohen-Aubart F, Dourmap C, Giral P, Bruckert E, et al. (2007) [Prevalence of sleep apnea in men with metabolic syndrome and controlled hypertension]. Arch Mal Coeur Vaiss 100: 637-641.
24. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, et al. (2005) American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung and Blood Institute Scientific Statement. Circulation 112: 2735-2752.
25. Ford ES, Li C, Zhao G (2010) Prevalence and correlates of metabolic syndrome based on a harmonious definition among adults in the US. J Diabetes 2: 180-193.
26. Beltrán-Sánchez H, Harhay MO, Harhay MM, McElligott S (2013) Prevalence and trends of metabolic syndrome in the adult U.S. population, 1999-2010. J Am Coll Cardiol 62: 697-703.
27. Kelly T, Yang W, Chen CS, Reynolds K, He J (2008) Global burden of obesity in 2005 and projections to 2030. Int J Obes (Lond) 32: 1431-1437.
28. Hu G, Qiao Q, Tuomilehto J, Balkau B, Borch-Johnsen K, et al. (2004) Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women. Arch Intern Med 164: 1066-1076.
29. Lemieux I, Pascot A, Couillard C, Lamarche B, Tchernof A, et al. (2000) Hypertriglyceridemic waist: A marker of the atherogenic metabolic triad (hyperinsulinemia; hyperapolipoprotein B; small, dense LDL) in men? Circulation 102:179-184.
30. Reaven GM (1988) Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 37: 1595-1607.
31. Ferrannini E, Haffner SM, Mitchell BD, Stern MP (1991) Hyperinsulinaemia: the key feature of a cardiovascular and metabolic syndrome. Diabetologia 34: 416-422.
32. Eckel RH, Grundy SM, Zimmet PZ (2005) The metabolic syndrome. Lancet 365: 1415-1428.
33. Eckel RH, Yost TJ, Jensen DR (1995) Alterations in lipoprotein lipase in insulin resistance. Int J Obes Relat Metab Disord 19 Suppl 1: S16-21.
34. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, et al. (2003) Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 112: 1796-1808.
35. Juhan-Vague I, Alessi MC, Mavri A, Morange PE (2003) Plasminogen activator inhibitor-1, inflammation, obesity, insulin resistance and vascular risk. J Thromb Haemost 1: 1575-1579.
36. Ruan H, Lodish HF (2004) Regulation of insulin sensitivity by adipose tissue-derived hormones and inflammatory cytokines. Curr Opin Lipidol 15: 297-302.
37. Diep QN, Amiri F, Touyz RM, Cohn JS, Endemann D, et al. (2002) PPARalpha activator effects on Ang II-induced vascular oxidative stress and inflammation. Hypertension 40: 866-871.
38. Pessler D, Rudich A, Bashan N (2001) Oxidative stress impairs nuclear proteins binding to the insulin responsive element in the GLUT4 promoter. Diabetologia 44: 2156-2164.
39. Dokken BB, Saengsirisuwan V, Kim JS, Teachey MK, Henriksen EJ (2008) Oxidative stress-induced insulin resistance in rat skeletal muscle: role of glycogen synthase kinase-3. Am J Physiol Endocrinol Metab 294: E615-621.
40. Ito Y, Oumi S, Nagasawa T, Nishizawa N (2006) Oxidative stress induces phosphoenolpyruvate carboxykinase expression in H4IIE cells. Biosci Biotechnol Biochem 70: 2191-2198.
41. Houstis N, Rosen ED, Lander ES (2006) Reactive oxygen species have a causal role in multiple forms of insulin resistance. Nature 440: 944-948.
42. Skalicky J, Muzakova V, Kandar R, Meloun M, Rousar T, et al. (2008) Evaluation of oxidative stress and inflammation in obese adults with metabolic syndrome. Clin Chem Lab Med 46: 499-505.
43. Poulsen P, Levin K, Petersen I, Christensen K, Beck-Nielsen H, et al. (2005) Heritability of insulin secretion, peripheral and hepatic insulin action, and intracellular glucose partitioning in young and old Danish twins. Diabetes 54: 275-283.
44. Boney CM, Verma A, Tucker R, Vohr BR (2005) Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics 115: e290-296.
45. Hanson MA, Gluckman PD (2008) Developmental origins of health and disease: new insights. Basic Clin Pharmacol Toxicol 102: 90-93.
46. Gungor Z, Anuurad E, Enkhmaa B, Zhang W, Kim K, et al. (2012) Apo E4 and lipoprotein-associated phospholipase A2 synergistically increase cardiovascular risk. Atherosclerosis 223: 230-234.
47. Basson J, Simino J, Rao DC (2012) Between candidate genes and whole genomes: time for alternative approaches in blood pressure genetics. Curr Hypertens Rep 14: 46-61.
48. Taylor JY, Sun YV, Hunt SC, Kardia SL (2010) Gene-environment interaction for hypertension among African American women across generations. Biol Res Nurs 12: 149-155.
49. Farooqi IS, O'Rahilly S (2004) Monogenic human obesity syndromes. Recent Prog Horm Res 59: 409-424.
50. Speakman JR, Rance KA, Johnstone AM (2008) Polymorphisms of the FTO gene are associated with variation in energy intake, but not energy expenditure. Obesity (Silver Spring) 16: 1961-1965.
51. Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D (2012) Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. Diabetes Care 35: 2402-2411.

52. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, et al. (2009) International Diabetes Federation Task Force on Epidemiology and Prevention; Hational Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. 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 120: 1640-1645.

53. Pothiwala P, Jain SK, Yaturu S (2009) Metabolic syndrome and cancer. Metab Syndr Relat Disord 7: 279-288.

54. Sertznig P, Seifert M, Tilgen W, Reichrath J (2007) Present concepts and future outlook: function of peroxisome proliferator-activated receptors (PPARs) for pathogenesis, progression, and therapy of cancer. J Cell Physiol 212: 1-12.

55. Hoeben A, Landuyt B, Highley MS, Wildiers H, Van Oosterom AT, et al. (2004) Vascular endothelial growth factor and angiogenesis. Pharmacol Rev 56: 549-580.

56. Barb D, Williams CJ, Neuwirth AK, Mantzoros CS (2007) Adiponectin in relation to malignancies: a review of existing basic research and clinical evidence. Am J Clin Nutr 86: s858-866.