



International Journal of Pharmacology

ISSN 1811-7775

science
alert

ansinet
Asian Network for Scientific Information

A Systematic Account of Pathogenesis, Diagnosis and Pharmacotherapy of Metabolic Syndrome: Things We Need to Know

¹R. Mahajan, ²K. Gupta and ¹V. Kapoor

¹Department of Pharmacology,

²Department of Biochemistry, Adesh Institute of Medical Sciences and Research,
Bathinda-151109 Punjab, India

Abstract: Metabolic Syndrome (MS) is a collection of risk factors including insulin resistance, central obesity, hypertension and dyslipidemia and itself is a risk factor for coronary artery disease. In recent times, its prevalence is on a rise in obese children too. Many working criteria for diagnosing MS are doing-the-round; given by World Health Organization, Adult Treatment Panel 3 and American Association of Clinical Endocrinologists. Risk factors involved in the pathogenesis of MS are many-fold; accordingly pharmacotherapy of MS is also multifacet. This review article is an account of pathogenesis, diagnosis and available treatment options in MS with a brief account of future prospect.

Key words: Hyperlipidemia, insulin resistance, obesity, type-2 diabetes

INTRODUCTION

The term Metabolic Syndrome (MS) was first time used by Haller (1977) to describe the associations of obesity, diabetes mellitus, hyperlipoproteinemia, hyperuricemia and steatosis hepatis when describing the additive effects of risk factors on atherosclerosis. It is one of the most discussed topics in the past 15 years due to its association with Coronary Heart Disease (CHD) (Sanchez-Torres and Delgado-Osorio, 1997). The MS, also known as cardiovascular dysmetabolic syndrome (Deedwania and Gupta, 2006), syndrome X, insulin resistance syndrome or Reaven's syndrome (Reaven, 1988), is a collection of risk factors that includes insulin resistance, central obesity, arterial hypertension and atherogenic dyslipidemia (Sanchez-Torres and Delgado-Osorio, 1997) and this cluster of abnormalities associated with insulin resistance identifies individuals at increased risk for cardiovascular disease (Kim and Reaven, 2004). It affects one in five people and prevalence increases with age. Some studies estimate the prevalence in the USA to be up to 25% of the population (Ford *et al.*, 2002; Meigs, 2003). The prevalence of MS is high among European obese children (12.2%) and this rapid rising prevalence of childhood obesity is related to increased risk of obesity-related diseases during adulthood (Bokor *et al.*, 2008). Given that India has the largest number of subjects with type-2 diabetes in the world it can be extrapolated that this country also has the largest

number of patients with the metabolic syndrome. Epidemiological studies confirm a high prevalence (Deedwania and Gupta, 2006).

SIGNS AND SYMPTOMS OF METABOLIC SYNDROME

Various characteristic features of MS include, but are not exclusively limited to:

- Fasting hyperglycemia-diabetes mellitus type 2 or impaired fasting glucose, impaired glucose tolerance, or insulin resistance (Vitale *et al.*, 2006)
- High blood pressure (Daskalopoulou *et al.*, 2004)
- Central obesity (also known as visceral, male-pattern or apple-shaped adiposity), overweight with fat deposits mainly around the waist (Daskalopoulou *et al.*, 2004).
- Elevated Triglycerides and LDL cholesterol; and decreased HDL cholesterol (Grundy, 2005)

Some associated diseases and signs may be there like hyperuricemia (Nakagawa *et al.*, 2006), fatty liver (especially in concurrent obesity) progressing to non-alcoholic fatty liver disease (Garcia-Compean *et al.*, 2009), polycystic ovarian syndrome (in women) (De Azevedo *et al.*, 2008) and erectile dysfunction and male hypogonadism (in men) (Corona *et al.*, 2008).

PATHOGENESIS OF METABOLIC SYNDROME

The metabolic syndrome seems to have 3 potential etiological categories: Obesity and disorders of adipose tissue, insulin resistance and a constellation of independent factors (molecules of hepatic, vascular and immunologic origin) that mediate specific components of the metabolic syndrome. Other factors-aging, proinflammatory state and hormonal changes have also been implicated as contributors (Grundy *et al.*, 2004).

Obesity and abnormal body fat distribution: Adult treatment panel 3 (ATP 3) considered the obesity epidemic as mainly responsible for the rising prevalence of metabolic syndrome. Obesity contributes to hypertension, high serum cholesterol, low HDL cholesterol and hyperglycemia and is otherwise associates with higher Cardio Vascular Disease (CVD) risk. Abdominal obesity especially correlates with metabolic risk factors. Excess adipose tissue releases several products like Non-Esterified Fatty Acids (NEFA), cytokines, Plasminogen Activator Inhibitor-1 (PAI-1) and adiponectin and these apparently exacerbate the risk factors (Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, 2001).

Insulin resistance: A second category of causation is insulin resistance. Many investigators place a greater priority on insulin resistance than on obesity in pathogenesis (Reaven, 1988; Ferrannini *et al.*, 1991). They argue that insulin resistance, or its accomplice, hyperinsulinemia, directly causes other metabolic risk factors. Identifying a unique role for insulin resistance is complicated by the fact that it is linked to obesity. Insulin resistance generally rises with increasing body fat content, yet a broad range of insulin sensitivities exists at any given level of body fat (Abbasi *et al.*, 2002). Most people with categorical obesity (body mass index [BMI]>30 kg m⁻²) have postprandial hyperinsulinemia and relatively low insulin sensitivity (Bogardus *et al.*, 1985).

Independent factors that mediate specific components of the metabolic syndrome: Beyond obesity and insulin resistance, each risk factor of the metabolic syndrome is subject to its own regulation through both genetic and acquired factors. This leads to variability in expression of risk factors. Lipoprotein metabolism, for instance, is richly modulated by genetic variation; hence, expression of dyslipidemias in response to obesity and/or insulin resistance varies considerably. The same holds for blood pressure regulation (Grundy *et al.*, 2004). Advancing age probably affects all levels of pathogenesis, which likely

explains why prevalence of the metabolic syndrome rises with advancing age (Ford *et al.*, 2002). Several members of a large family of nonselective cation-entry channels, like Transient Receptor Potential (TRP) Canonical (TRPC), Vanilloid (TRPV) and Melastatin (TRPM) channels, have been associated with the development of cardiovascular diseases. TRPV1 regulates adipogenesis and inflammation in adipose tissues, whereas TRPC3, TRPC5, TRPC6, TRPV1 and TRPM7 are involved in vasoconstriction and regulation of blood pressure. Other members of the TRP family are involved in regulation of insulin secretion, lipid composition and atherosclerosis. Thus, disruption of TRP channel expression or function may account for the observed increased cardiovascular risk in metabolic syndrome patients (Liu *et al.*, 2008). Even oxidative stress due to a variety of causes including increased uric acid levels caused by dietary fructose has been implicated in the pathogenesis of MS (Nakagawa *et al.*, 2006).

CRITERIA FOR CLINICAL DIAGNOSIS OF METABOLIC SYNDROME

At least 3 organizations have recommended clinical criteria for the diagnosis of the metabolic syndrome. Their criteria are similar in many aspects, but they also reveal fundamental differences in positioning of the predominant causes of the syndrome.

Adult treatment panel (atp) iii criteria: Criteria of ATP 3 are shown in Table 1 (NECP, Expert Panel, 2001). When 3 of 5 of the listed characteristics are present, a diagnosis of metabolic syndrome can be made. The primary clinical outcome of metabolic syndrome was identified as CHD/CVD.

Abdominal obesity, recognized by increased waist circumference, is the first criterion listed. Explicit demonstration of insulin resistance is not required for diagnosis; however, most persons meeting ATP 3 criteria will be insulin resistant.

World health organization criteria: In 1998, a World Health Organization (WHO) consultation group outlined

Table 1: ATP 3 clinical identification of the metabolic syndrome

Risk factor	Defining level
Abdominal obesity, given as waist circumference	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides HDL cholesterol	≥150 mg dL ⁻¹
Men	<40 mg dL ⁻¹
Women	<50 mg dL ⁻¹
Blood pressure	≥130/≥85 mm of Hg
Fasting glucose	≥10 mg dL ⁻¹ #

#After ATP 3 criteria were established, the American Diabetic Association changed cut-off point to of fasting glucose to ≥100 mg dL⁻¹ (Genuth *et al.*, 2003) Accordingly, this cut-off should be considered for diagnosing Metabolic Syndrome

Table 2: WHO clinical criteria for metabolic syndrome

Insulin resistance, identified by one of the following	
<ul style="list-style-type: none"> • Type 2 diabetes • Impaired fasting glucose • Impaired glucose tolerance • or for those with normal fasting glucose levels, glucose uptake below the lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions 	
Plus any two of the following	
<ul style="list-style-type: none"> • Antihypertensive medication and high blood pressure ($\geq 140/\geq 90$ mm of Hg) • Plasma triglycerides ≥ 150 mg dL⁻¹ • HDL cholesterol < 35 mg dL⁻¹ in men or < 39 mg dL⁻¹ in women • BMI > 30 kg m⁻² and/or waist:hip ratio > 0.9 in men, > 0.85 in women • Urinary albumin excretion rate $20 \mu\text{g min}^{-1}$ or albumin:creatinine ratio ≥ 30 mg g⁻¹ 	

Table 3: AACE clinical criteria for diagnosis of the metabolic syndrome

Risk factor component	Cut-off points for abnormality
Overweight/obesity	BM ≥ 25 kg m ²
Elevated triglycerides	≥ 150 mg dL ⁻¹
Low HDL cholesterol	
Men	< 40 mg dL ⁻¹
Women	< 50 mg dL ⁻¹
Elevated blood pressure	$\geq 130/85$ mm of Hg
2-hour post-glucose challenge	> 140 mg dL ⁻¹
Fasting glucose	Between 110 and 126 mg dL ⁻¹
Other risk factors	
<ul style="list-style-type: none"> • Family history of type 2 diabetes, hypertension or cardiovascular disease • Polycystic ovarian syndrome • Sedentary life style, advancing age • Ethnic groups having high risk for type 2 diabetes or CVD 	

a provisional classification of diabetes that included a working definition of the metabolic syndrome (Alberti and Zimmet, 1998), which was finalized in 1999. The guideline group also recognized CVD as the primary outcome of the metabolic syndrome. However, it viewed Insulin Resistance (IR) as a required component for diagnosis. In addition to IR, 2 other risk factors are sufficient for a diagnosis of metabolic syndrome (Table 2).

American association of clinical endocrinologists criteria: The American Association of Clinical Endocrinologists (AACE) proposes a third set of clinical criteria for the insulin resistance syndrome (Einhorn *et al.*, 2003). These criteria appear to be a hybrid of those of ATP 3 and WHO metabolic syndrome. However, no defined number of risk factors is specified; diagnosis is left to clinical judgment (Table 3).

METABOLIC SYNDROME AS A RISK CONDITION

It seems self-evident that a condition characterized by multiple risk factors will carry a greater risk for adverse clinical outcomes than with a single risk factor. Individuals with metabolic syndrome are at increased risk for CHD (Lakka *et al.*, 2002). In Framingham, the metabolic syndrome alone predicted ~25% of all new-onset CVD. When the risk for new-onset diabetes was

examined for the Framingham cohort, in both men and women, the presence of metabolic syndrome was highly predictive of new-onset diabetes. Almost half of the population-attributable risk for diabetes could be explained by the presence of ATP 3 metabolic syndrome.

THERAPEUTIC STRATEGIES AND IMPLICATIONS

The two major therapeutic strategies for treatment of affected persons are prevention by modification of the underlying risk factors and separate drug treatment of the particular metabolic risk factors when appropriate.

Prevention: Various strategies proposed to prevent the development of metabolic syndrome include, increased physical activity (such as walking 30 min every day) or aerobic exercises (Lakka and Laaksonen, 2007); (Katzmarzyk *et al.*, 2003) and a healthy, reduced calorie diet with evidence of beneficial effects of replacing some carbohydrate with monounsaturated fat (Feldeisen and Tucker, 2007). Physical exercise have an independent effect on glycemia control, insulin sensitivity, serum lipid levels, blood pressure, weight reduction and in promoting psychological well being (Spellman, 2009; Shehu *et al.*, 2010). The International Obesity Taskforce states that interventions on a sociopolitical level are required to reduce development of the metabolic syndrome in populations (James *et al.*, 2004).

A 2007 study of 2,375 male subjects over 20 years suggested that daily intake of a pint of milk or equivalent dairy products, more than halved the risk of metabolic syndrome (Elwood *et al.*, 2007; Snijder *et al.*, 2007). It has been shown that green tea, when consumed on a daily basis, has favorable effects on the major MS risk factors such as obesity, type-2 diabetes and cardiovascular risk factors (Thielecke and Boschmann, 2009).

Pharmacotherapy: Drug therapy is needed to achieve recommended goals if therapeutic lifestyle changes are not sufficient. As the cause of Metabolic Syndrome is multifactorial, treatment should also be multifacet (Liberopoulos *et al.*, 2005). Various targets of pharmacotherapy and the drugs used in Metabolic Syndrome include:

Obesity as target of pharmacotherapy: Other than weight loss, there is no single best therapy for Metabolic Syndrome (Deedwania and Gupta, 2006). This weight loss can be achieved by using therapeutic lifestyle approaches, as mentioned earlier (diet control and increased physical activity), for control of obesity and

visceral obesity or by pharmacotherapy using anti-obesity agents. Weight loss lowers serum cholesterol and triglycerides, raises HDL cholesterol, lowers blood pressure and glucose and reduces insulin resistance. Recent data further show that weight reduction can decrease serum levels of C-Reactive Protein (CRP) and PAI-1 (Grundy *et al.*, 2004). Short term weight loss can be achieved, but keeping this weight off can be a problem. It often requires making exercise and a lower calorie diet a permanent part of a person's lifestyle (Shick *et al.*, 1998; Tate *et al.*, 2007). In the general population only 20% people are successful at long-term weight loss maintenance (Wing and Phelan, 2005).

Only two anti-obesity medications are currently approved by the FDA for long term use. One is orlistat, which reduces intestinal fat absorption by inhibiting pancreatic lipase; the other is sibutramine, which acts in the brain to inhibit deactivation of the neurotransmitters norepinephrine, serotonin and dopamine, therefore decreasing appetite. However, their safety and effectiveness have not been established for use beyond 2 years (WIN, 2007). Rimonabant, a third drug, works via a specific blockade of the endocannabinoid system and has been developed from the knowledge that cannabis smokers often experience extreme hunger pangs, which are often referred to as the munchies. It has been approved in Europe for the treatment of obesity but has not yet received approval in the United States or Canada due to safety concerns (CBC News, 2007; FDA, 2007).

Even with these drugs weight loss is modest. Over a long term, average weight loss with orlistat is 2.9 kg, with sibutramine it is 4.2 kg and with rimonabant it is 4.7 kg. Orlistat and rimonabant lead to a reduced incidence of diabetes and all three drugs have some cholesterol lowering effect. There is however little data on how these drugs affect the longer-term complications or outcomes of obesity (Rucker *et al.*, 2007).

Bariatric surgery is only recommended for severely obese people (BMI>40) who have failed to lose weight with dietary modification and pharmacological treatment. This can be done by reducing the volume of the stomach or by producing an earlier sense of satiation (by adjustable gastric banding and vertical banded gastroplasty) or by reducing the length of bowel that food will be in contact with, directly reducing absorption known as gastric bypass surgery (Encinosa *et al.*, 2006). A marked decrease in the risk of diabetes mellitus, cardiovascular disease and cancer has also been found after bariatric surgery (Sjostrom, 2008).

Insulin resistance and hyperglycemia as target of pharmacotherapy: The primary treatment for insulin resistance is also exercise, weight loss and low-

carbohydrate diets (Boden *et al.*, 2005). Both metformin and the thiazolidinediones improve insulin resistance, but are only approved therapies for type 2 diabetes, not insulin resistance, *per se*. A recent study has reported metformin to be more efficacious and cost-effective insulin sensitizer as compared to pioglitazone in patients with metabolic syndrome (Mahajan *et al.*, 2010).

Metformin is the only anti-diabetic drug that has been proven to protect against the cardiovascular complications of diabetes (Selvin *et al.*, 2008). Additional advantage with metformin is its capacity to cause minor weight loss (Stumvoll *et al.*, 1995). It modestly reduces LDL and triglyceride levels also (Bolen *et al.*, 2007). Development of hypoglycemia is not a problem with metformin (Kilo *et al.*, 2003). Thiazolidinediones (TZDs) improve glycemic control and insulin sensitivity in patients with type 2 diabetes, despite their potential to cause weight gain, due to favourable redistribution of body fats (Fonseca, 2003). Pioglitazone (a thiazolidinedione) treatment has shown significant protection from both micro-vascular and macro-vascular cardiovascular events and plaque progression (Mannucci *et al.*, 2008).

There are, however, no CVD end-point studies on metformin or TZDs treated patients with metabolic syndrome. Thus, at present, metformin or TZDs cannot be recommended for the express purpose of reducing risk for CVD in persons with the metabolic syndrome (Grundy *et al.*, 2004). It is documented that omega-3 fatty acids can also improve insulin sensitivity (Lovejoy, 2002). When there is no insulin resistance, any oral antidiabetic agent like metformin, TZDs, acarbose, meglitinide can be used for controlling blood glucose levels within normal limits (Liberopoulos *et al.*, 2005). Glucagon like peptide-1 receptor agonists like exenatide and dipeptidyl peptidase 4 inhibitors like vildagliptin are new insulin secretagogues which have been recommended to be used in type 2 diabetic patients, by American Diabetes association and UK's National Institute of Clinical Excellence (Mahajan and Gupta, 2010a).

Atherogenic dyslipidemia as target of pharmacotherapy:

Although statins typically are recognized to be LDL-lowering drugs, they reduce all apolipoprotein B containing lipoproteins. Recent subgroup analysis of statin trials reveal that statins reduce risk for CVD events in patients with metabolic syndrome. Fibrates also favorably modify atherogenic dyslipidemia and may directly reduce atherogenesis. Post hoc analysis of recent fibrate trials strongly suggests that they reduce CVD end points in patients with atherogenic dyslipidemia and metabolic syndrome (Rubins, 2000). Statins do not

improve insulin resistance (Clough *et al.*, 2009) while fibrates are known to increase insulin sensitivity and this may be an additional mechanism by which they decrease incidence of coronary heart disease in metabolic syndrome (Han *et al.*, 2005). Fibrates are recommended as an adjunct to statins for treatment of residual dyslipidemia and residual CVD risk, but this combination may, however, raise the risk of myopathy and rhabdomyolysis (Briton, 2008).

Elevated blood pressure as target of pharmacotherapy:

Treatment of categorical hypertension in patients with MS with drugs has become standard practice (Grundy, 2005). The blood pressure target is <140/90 mm Hg. The effect on carbohydrate homeostasis should possibly be taken into account in selecting an antihypertensive drug (Daskalopoulou *et al.*, 2004). Available evidence suggests that Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs) are more beneficial for treatment of hypertension in patients with MS compared to others as these drugs also prevent development of diabetes (Deedwania and Gupta, 2006). Alternatives are, calcium channel blocker or addition of a low dose of a thiazide diuretic if necessary (Liberopoulos *et al.*, 2005).

Prothrombotic state as target of pharmacotherapy: No drugs are available that target PAI-1 and fibrinogen. An alternative approach to the prothrombotic state is antiplatelet therapy. Aspirin which has an antiplatelet or anti-clotting, effect is used in long-term, low doses to prevent heart attacks, strokes and blood clot formation in people at high risk for developing blood clots (Lewis *et al.*, 1983).

Other targets of pharmacotherapy: These include, targeting proinflammatory state by reducing C-reactive protein with the use of lipid lowering drugs (Grundy *et al.*, 2004), improving liver function in nonalcoholic fatty liver disease and a reducing the risk of acute gout (Daskalopoulou *et al.*, 2004).

Future trends in pharmacotherapy: In a recent study, Phosphodiesterase-5-inhibitor Tadalafil in a dose of 10 mg d⁻¹ has shown to improve β -cell function after 3week treatment and may prove to be a novel strategy for improving β -cell function in metabolic syndrome (Hill *et al.*, 2009).

Rivoglitazone, an insulin sensitizer with peroxisome proliferator-activated receptor gamma agonistic activity is currently under development for the potential treatment of

type 2 diabetes (Schimke and Davis, 2007). Similarly, tiplaxtinin, a selective plasminogen activator inhibitor-1 is undergoing clinical trials (Elokda *et al.*, 2004).

Recent studies have linked type-2 diabetes with deranged circadian rhythm and a possible link between circadian rhythm regulation and glucose homeostasis through the melatonin signaling pathway has been suspected (Kapoor and Mahajan, 2009). Thus, melatonin pathway may prove to be a novel base for the development of type 2 diabetes. Bromocriptine mesylate, a recently introduced drug for type 2 diabetes also act by resetting the deranged circadian rhythm and has proved useful in patients with insulin resistance (Mahajan, 2009). Bromocriptine may prove useful in MS also.

In a recent experimental study, it has been shown that severe myostatin deficiency caused by Ln mutations; even in high fat diet fed mice protect muscle and liver against obesity-induced insulin resistance (Wilkes *et al.*, 2009). So, myostatin gene can be a good target for designing new drugs for the treatment of IR and MS.

Another area of interest is the development of dual peroxisome proliferator-activated receptor agonists. The PPAR alpha/gamma dual agonists are being developed to increase insulin sensitivity and simultaneously prevent diabetic cardiovascular complications. Such compounds are under clinical trials and proposed for treatment of type-2 diabetes with secondary cardiovascular complications (Mahajan and Gupta, 2010b). As these compounds are intended to target both type-2 diabetes and cardiovascular complications, they may prove efficacious in MS.

CONCLUSION

Despite the assertion that different sets of conflicting and incomplete diagnostic criteria are in existence for Metabolic Syndrome and that the metabolic syndrome is nothing more than the sum of its constituent parts and despite questioning its clinical value (Kahn, 2008), it is agreed that CVD is the primary outcome of MS, with additional risk of type 2 diabetes, which itself is a risk factor for CVD. Life style changes with emphasis on weight reduction constitute the 1st line therapy for MS. Drug treatment for component traits is known to reduce the risk for type 2 diabetes and CVD; whether risk is reduced by treatment of the syndrome, specifically, remains uncertain (Meigs, 2002). Fixed-dose combination-polypharmacy using a single pill is an interesting concept that needs to be evaluated in long-term prospective trials in patients with Metabolic Syndrome.

REFERENCES

- Abbasi, F., B.W. Brown Jr, C. Lamendola, T. McLaughlin and G.M. Reaven, 2002. Relationship between obesity, insulin resistance and coronary heart disease risk. *J. Am. Coll. Cardiol.*, 40: 937-943.
- Alberti, K.G. and P.Z. Zimmet, 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. *Diabetic Med.*, 15: 539-553.
- Boden, G., K. Sargrad, C. Homko, M. Mozzoli and T.P. Stein, 2005. Effect of a low-carbohydrate diet on appetite, Blood glucose levels and insulin resistance in obese patients with type 2 diabetes. *Ann. Intern. Med.*, 142: 403-411.
- Bogardus, C., S. Lillioja, D.M. Mott, C. Hollenbeck and G. Reaven, 1985. Relationship between degree of obesity and *in vivo* insulin action in man. *Am. J. Physiol.*, 248: e286-e291.
- Bokor, S., M.L. Frelut, A. Vania, C.G. Hadjiathanasiou and M. Anastasakou *et al.*, 2008. Prevalence of metabolic syndrome in European obese children. *Int. J. Pediatr. Obes.*, 3: 3-8.
- Bolen, S., L. Feldman, J. Vassy, L. Wilson, H.C. Yeh and S. Marinopoulos *et al.*, 2007. Systematic review: Comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann. Int. Med.*, 147: 386-399.
- Briton, E.A., 2008. Does the addition of fibrates to statin therapy have favorable risk to benefit ratio. *Curr. Atheroscler. Rep.*, 10: 25-32.
- CBC News, 2007. Anti-obesity drug no magic bullet. <http://www.cbc.ca/health/story/2007/01/02/rimona bant.html>.
- Clough, G., M. Turzyniecka, L. Walter, A.J. Krentz and S.H. Wild *et al.*, 2009. Muscle microvascular dysfunction in central obesity is related to muscle insulin insensitivity but is not reversed by high-dose Statin treatment. *Diabetes.*, 58: 1185-1191.
- Corona, G., G. Forti and M. Maggi, 2008. Why can patients with erectile dysfunction be considered lucky The association with testosterone deficiency and metabolic syndrome. *Aging Male.*, 11: 193-199.
- Daskalopoulou, S.S., D.P. Mikhailidis and M. Elisaf, 2004. Prevention and treatment of the metabolic syndrome. *Angiology*, 55: 589-612.
- De Azevedo, G.D., E.C. Costa, M.T. Micussi and J.C. de Sa, 2008. Lifestyle modifications in polycystic ovary syndrome: role of physical exercise and importance of multidisciplinary approach (Article in Portuguese). *Rev. Bras. Gynecol. Obstet.*, 30: 261-267.
- Deedwania, P.C. and R. Gupta, 2006. Management issues in the metabolic syndrome. *J. Assoc. Physicians. India*, 54: 797-810.
- Einhorn, D., G.M. Reaven, R.H. Cobin, E. Ford and O.P. Ganda *et al.*, 2003. American College of Endocrinology position statement on the insulin resistance syndrome. *Endocr. Pract.*, 9: 237-252.
- Elokda, H., M. Abou-Gharbia, J.K. Hannan, G. McFarlane, C.P. Mugford, G. Krishnamurthy and D.L. Crandall, 2004. Tiplaxtinin, a novel, orally efficacious inhibitor of plasminogen activator inhibitor-1: design, synthesis and preclinical characterization. *J. Med. Chem.*, 47: 3491-3494.
- Elwood, P.C., J.E. Pickering and A.M. Fehily, 2007. Milk and dairy consumption, diabetes and the metabolic syndrome: the Caerphilly prospective study. *J. Epidemiol. Community Health*, 61: 695-698.
- Encinosa, W.E., D.M. Bernard, C.C. Chen and C.A. Steiner, 2006. Healthcare utilization and outcomes after bariatric surgery. *Med. Care*, 44: 706-712.
- Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, 2001. 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). *J. Am. Med. Assoc.*, 285: 2486-2497.
- FDA, 2007. FDA, 2007. FDA briefing document NDA 21-888: Zimulti (rimonabant) tablets, 20 mg. <http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4306b1-fda-backgrounder.pdf>.
- Feldeisen, S.E. and K.L. Tucker, 2007. Nutritional strategies in the prevention and treatment of metabolic syndrome. *Applied Physiol. Nutr. Metab.*, 32: 46-60.
- Ferrannini, E., S.M. Haffner, B.D. Mitchell and M.P. Stern, 1991. Hyperinsulinaemia: The key feature of a cardiovascular and metabolic syndrome. *Diabetologia*, 34: 416-422.
- Fonseca, V., 2003. Effects of thiazolidinediones on body weight in patients with diabetes mellitus. *Am. J. Med.*, 115: 42S-48S.
- Ford, E.S., W.H. Giles and W.H. Dietz, 2002. Prevalence of metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA*, 287: 356-359.
- Garcia-Compean, D., J.O. Jaquez-Quintana, J.A. Gonzalez-Gonzalez and H. Maldonado-Garza, 2009. Liver cirrhosis and diabetes: Risk factors, pathophysiology, clinical implications and management. *World J. Gastroenterol.*, 15: 280-288.

- Genuth, S., K.G. Alberti, P. Bennett, J. Buse and R. Defronzo *et al.*, 2003. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care*, 26: 3160-3167.
- Grundy, S.M., H.B. Brewer, J.I. Cleeman, S.C. Smith, Jr. C. Lenfant and American Heart Association, National Heart Lung and Blood Institute, 2004. Definition of metabolic syndrome: Report of the National, Heart, Lung and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation*, 109: 433-438.
- Grundy, S.M., 2005. Metabolic syndrome: Therapeutic considerations. *Handbook Exp. Pharmacol.*, 170: 107-133.
- Haller, H., 1977. Epidemiology and associated risk factors of hyperlipoproteinemia (Article in German). *Z. Gesamte. Inn. Med.*, 32: 124-128.
- Han, S.H., M.J. Ounou and K.K. Koh, 2005. Beneficial vascular and metabolic effects of peroxisome proliferator activated receptor- α activators. *Hypertension*, 46: 1086-1092.
- Hill, K.D., A.W. Eckhauser, A. Marney and N.J. Brown, 2009. Phosphodiesterase 5 inhibition improves beta cell function in the metabolic syndrome. *Diabetes Care*, 32: 857-859.
- James, P.T., N. Rigby, R. Leach and International Obesity Task Force, 2004. The obesity epidemic, metabolic syndrome and future prevention strategies. *Eur. J. Cardiovasc. Prev. Rehabil.*, 11: 3-8.
- Kahn, R., 2008. Metabolic syndrome-what is the clinical usefulness?. *Lancet*, 371: 1892-1893.
- Kapoor, V. and R. Mahajan, 2009. Chronotherapeutics. *JK Sci.: J. Med. Edu. Res.*, 11: 109-110.
- Katzmarzyk, P.T., A.S. Leon, J.H. Wilmore, J.S. Skinner, D.C. Rao, T. Rankinen and C. Bouchard, 2003. Targeting the metabolic syndrome with exercise: Evidence from the heritage family study. *Med. Sci. Sports Exerc.*, 35: 1703-1709.
- Kilo, C., N. Mezitis, R. Jain, J. Mersey, J. McGill and P. Raskin, 2003. Starting patients with type 2 diabetes on insulin therapy using once-daily injections of biphasic insulin aspart 70/30, biphasic human insulin 70/30, or NPH insulin in combination with metformin. *J. Diabetes Complications*, 17: 307-313.
- Kim, S.H. and G.M. Reaven, 2004. The metabolic syndrome: one step forward, two step back. *Diab. Vasc. Dis. Res.*, 1: 68-75.
- Lakka, H.M., D.E. Laaksonen, T.A. Lakka, L.K. Niskanen, E. Kumpusalo, J. Tuomilehto and J.T. Salonen, 2002. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *J. Am. Med. Assoc.*, 288: 2709-2716.
- Lakka, T.A. and D.E. Laaksonen, 2007. Physical activity in prevention and treatment of the metabolic syndrome. *Applied Physiol. Nutr. Metab.*, 32: 76-88.
- Lewis, Jr. H.D., J.W. Davis, D.G. Archibald, W.E. Steinke and T.C. Smitherman *et al.*, 1983. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina: Results of a Veterans administration cooperative study. *N. Engl. J. Med.*, 309: 396-403.
- Liberopoulos, E.N., D.O. Mikkilaidis and M.S. Elisaf, 2005. Diagnosis and management of the metabolic syndrome in obesity. *Obes. Rev.*, 6: 283-296.
- Liu, D., Z. Zhu and M. Tepel, 2008. The role of transient receptor potential channels in metabolic syndrome. *Hypertens. Res.*, 31: 1989-1995.
- Lovejoy, J.C., 2002. The influence of dietary fat on insulin resistance. *Curr. Diab. Rep.*, 2: 435-440.
- Mahajan, R., 2009. Bromocriptine mesylate: FDA-approved novel treatment for type-2 diabetes. *Indian J. Pharmacol.*, 41: 197-198.
- Mahajan, R. and K. Gupta, 2010a. Drugs in pipeline for type-2 diabetes. *Internet J. Pharmacol.*, Vol. 8(2). http://www.ispub.com/journal/the_internet_journal_of_pharmacology/volume_8_number_2_19/article/drugs-in-pipeline-for-type-2-diabetes.html
- Mahajan, R. and K. Gupta, 2010b. Incretin mimetics and enhancers: New insulin secretagogues for type-2 diabetes. *Biomed. Res.*, 21: 99-105.
- Mahajan, R., A.K. Gupta, K. Gupta, V. Kapoor, R.S. Gupta and G.K. Bedi, 2010. Efficacy and cost-effectiveness of insulin sensitizers in metabolic syndrome: A randomized control trial. *Inventi Rapid: Clin. Pharm.*, Vol. 1(1).
- Mannucci, E., M. Monami, C. Lamanna, G.F. Gensini and N. Marchionni, 2008. Pioglitazone and cardiovascular risk. A comprehensive meta-analysis of randomized clinical trials. *Diabetes Obes. Metab.*, 10: 1221-1238.
- Meigs, J.B., 2002. Epidemiology of the metabolic syndrome, 2002. *Am. J. Manage. Care.*, 8: S283-292.
- Meigs, J.B., 2003. Epidemiology of insulin resistance syndrome. *Curr Diab Rep.*, 3: 73-79.
- Nakagawa, T., H. Hu, S. Zharikov, K.R. Tuttle and R.A. Short *et al.*, 2006. A causal role for uric acid in fructose-induced metabolic syndrome. *Am. J. Physiol. Renal Physiol.*, 290: F625-F631.
- Reaven, G.M., 1988. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes*, 37: 1595-1607.
- Rubins, H.B., 2000. Triglycerides and coronary heart disease: implications of recent clinical trials. *J. Cardiovasc. Risk.*, 7: 339-345.
- Rucker, D., R. Padwal, S.K. Li, C. Curioni and D.C. Lau, 2007. Long term pharmacotherapy for obesity and overweight: Updated meta-analysis. *BMJ*, 335: 1194-1199.

- Sanchez-Torres, R.J. and H. Delgado-Osorio, 1997. The metabolic syndrome and its cardiovascular manifestations. *Bol. Asoc. Med. P. R.*, 4: 271-280.
- Schimke, K. and T.M. Davis, 2007. Drug evaluation: Rivoglitazone, a new oral therapy for the treatment of type 2 diabetes. *Curr. Opin. Investig. Drugs.*, 8: 338-344.
- Selvin, E., S. Bolen, H.C. Yeh, C. Wiley and L.M. Wilson *et al.*, 2008. Cardiovascular outcomes in trials of oral diabetes medications: A systematic review. *Arch. Int. Med.*, 168: 2070-2080.
- Shehu, R.A., S.A. Onasanya, T.A. Oloyede and M. Kinta, 2010. Contribution of information and communication technology to the prevalence of obesity and elevated blood pressure among secondary school students in Nigeria. *J. Applied Sci.*, 10: 359-362.
- Shick, S.M., R.R. Wing, M.L. Klem, M.T. McGuire, J.O. Hill and H. Seagle, 1998. Persons successful at long-term weight loss and maintenance continue to consume a low-energy, low-fat diet. *J. Am. Diet. Assoc.*, 98: 408-413.
- Sjostrim, L., 2008. Bariatric surgery and reduction in morbidity and mortality: Experiences from the SOS study. *Int. J. Obes. (London)*, 31: S93-S97.
- Snijder, M.B., A.A. van der Heijden, R.M. van Dam, C.D. Stehouwer and G.J. Hiddink *et al.*, 2007. Is higher dairy consumption associated with lower body weight and fewer metabolic disturbances? The Hoorn Study. *Am. J. Clin. Nutr.*, 85: 989-995.
- Spellman, C.W., 2009. Achieving glycemic control: Cornerstone is the treatment of patients with multiple metabolic risk factors. *J. Am. Osteopath. Assoc.*, 109: S8-S13.
- Stumvoll, M., N. Nurjhan, G. Perriello, G. Dailey and J.E. Gerich, 1995. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. *N. Engl. J. Med.*, 333: 550-554.
- Tate, D.F., R.W. Jeffery, N.E. Sherwood and R.R. Wing, 2007. Long-term weight losses associated with prescription of higher physical activity goals. Are higher levels of physical activity protective against weight regain?. *Am. J. Clin. Nutr.*, 85: 954-959.
- Thielecke, F. and M. Boschmann, 2009. The potential role of green tea catechins in the prevention of the metabolic syndrome: A review. *Phytochemistry*, 70: 11-24.
- Vitale, C., G. Marazzi, M. Volterrani, A. Aloisio, G. Rosano and M. Fini, 2006. Metabolic syndrome. *Minerva Med.*, 97: 219-229.
- WIN, 2007. Prescription medications for the treatment of obesity. Weight-control Information Network. <http://win.niddk.nih.gov/publications/prescription.htm#fdameds>.
- Wilkes, J.J., D.J. Lloyd and N. Gekakis, 2009. Loss-of-function mutation in myostatin reduces TNF-alpha production and protects liver against obesity-induced insulin resistance. *Diabetes*, 58: 1133-1143.
- Wing, R.R. and S. Phelan, 2005. Long-term weight loss maintenance. *Am. J. Clin. Nutr.*, 82: 222S-225S.