ISSN 0975 - 6299 Vol 2 / Issue 4 / Oct - Dec 2011

International Journal of Pharma and Bio Sciences

REVIEW ARTICLE MOLECULAR BIOLOGY

REVIEW OF METABOLIC SYNDROME: A RISING MENACE

DR. DIPTI MOHAPATRA*[1] AND DR. PRAKASH KR. SASMAL[2]

[1]Department of Physiology, IMS &SUM Hospital, SOA University, Bhubaneswar, India
[2]Department of Surgery, IMS &SUM Hospital, SOA University, Bhubaneswar, India.

DR. DIPTI MOHAPATRA
Department of Physiology, IMS &SUM Hospital, SOA University, Bhubaneswar, India

*Corresponding author

ABSTRACT

The prevalence of obesity, a major risk factor of metabolic syndrome is increasing in frightening proportions worldwide in all the age groups. Multiple diseases or co-morbidities associated with obesity are termed the “Metabolic Syndrome,” or “Syndrome X”. Resistance to insulin is the central feature of the metabolic syndrome. Increased tendency to develop central obesity makes Asian Indians prone to develop metabolic syndrome, which has resulted in the growing epidemic of type 2 diabetes and coronary heart disease currently sweeping the Indian subcontinent. The current modalities of treatment of metabolic syndrome include diet, exercise and pharmacotherapy. Life-style modification programmes that promote daily physical activity and healthy eating devoid of saturated fat and processed carbohydrate are desperately needed to tackle this growing menace. Using Bariatric surgery explicitly to treat metabolic disorders including diabetes is a revolutionary concept and represents a disruption to current therapeutic paradigms.

ISSN 0975 - 6299 Vol 2 / Issue 4 / Oct - Dec 2011

KEYWORDS

Central Obesity, Insulin resistance, Life style modifications and Bariatric surgery.

INTRODUCTION

The metabolic syndrome in adults has been defined as a cluster of the most dangerous risk factors for cardiovascular disease and type 2 diabetes, which include abdominal obesity, hypertension, high cholesterol and fasting plasma glucose.

The Indian subcontinent is undergoing significant epidemiological transition as non-communicable diseases like coronary heart disease and type 2 diabetes mellitus are fast replacing infections as the leading cause of morbidity and mortality. India by 2025 is predicted to become the global capital for Diabetes and as estimated over 300 million affected individuals by the year 2025, the lifetime risk of developing type 2 diabetes will approximate 20%[1]. Clustering together of hypertension, central (upper body or android) obesity, and dyslipidaemia, with or without hyperglycaemia is recognised for many decades and has been prospectively demonstrated in the Framingham Study in the 1970s, and the Scandinavian Studies in the 1980s[2]. Gerald Reaven was the first scientist to name this cluster as Syndrome X in 1988[3].

Although the components of the metabolic syndrome were first described over 40 years ago, it was only recently that both the World Health Organization (WHO) and the United States (US) National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III provided a clinical definition of the syndrome.

Obesity is a recognised cause of insulin resistance (IR) that leads to impaired glucose tolerance. Resistance to insulin is the central feature of metabolic syndrome, which is linked predominantly to a cluster of disorders involving triglycerides and glucose metabolism, hypertension and micro-angiopathy.

The metabolic syndrome appears to affect between 10 to 25 percent of adult population worldwide[1]. The prevalence of the metabolic syndrome is likely to increase with increasing prevalence of obesity and will contribute to the epidemic of diabetes that has been described[4].

This review article deals with the recent knowledge gained in understanding the aetiopathogenesis of metabolic syndrome and the present evidence available for its prevention as well as management - especially surgical treatment.

METABOLIC SYNDROME- DEFINITION

Although metabolic syndrome is now a well-recognised entity, its true prevalence varies widely in different studies mainly because of lack of universally accepted criteria defining the syndrome. A multitude of studies have shown that excess fat in the abdominal region (visceral adipose tissue) is strongly associated with metabolic alterations such as disturbed plasma lipoprotein profile, hyperinsulinemia, insulin resistance and glucose intolerance[1,5]. It is not essential for all elements of this syndrome to be present in a single patient. The distribution of fat, rather than overall obesity, determines risk. The reported association between increased abdominal (upper body) fat and an increased risk of coronary heart disease relates to visceral fat, for which the waist-to-hip ratio is a convenient index. A waist-to-hip ratio of greater than 1.0 in men and 0.8 in women indicates abdominal obesity.

Neel (1962) proposed the 'thrifty genotype' hypothesis to explain the emergence of insulin resistance and diabetes in populations shifting from vigorous activity and subsistence nutrition to abundance and obesity of urban societies[6].

In 1999, WHO proposed a working definition (Table 1) and the name of the syndrome was changed to metabolic syndrome primarily because central obesity was not included in the original description by Reaven.

Table 1
WHO's working definition of metabolic syndrome.

- Impaired glucose regulation, or diabetes.
- Insulin resistance (under hyperinsulinaemic euglycaemic conditions, glucose uptake below lowest quartile for background population under investigation).
- Raised arterial pressure ≥ 140/90 mmHg.
- Raised plasma triglyceride (≥ 150 mg/dl) and/or low HDL cholesterol (< 35 mg/dl for men; < 39 mg/dl for women).
- Central obesity (men: waist to hip ratio > 0.90; females: waist to hip ratio > 0.85) and/or BMI > 30 Kg/m2.
- Microalbuminuria (urea albumin excretion rate ≥ 20 µg/min or albumin: creatinine ratio ≥ 30 mg/g.

Diagnosis of metabolic syndrome is made when two or more of the above-mentioned components are present in presence of impaired glucose regulation or diabetes mellitus and/or insulin resistance.

It is important to take note of two facts in the WHO description:

1. Each component of the syndrome conveys increased cardiovascular risk, but as a combination they become much more powerful.
2. The features of metabolic syndrome may be present for upto 10 years before detection of glycaemic disorders.

The 2001 national cholesterol education programme adult treatment panel guidelines (NCEP ATP III) [7] define metabolic syndrome differently (Table II).

Table II
ATP III criteria for identification of metabolic syndrome.

- Abdominal obesity (waist circumference): Men > 102 cm (40 in); Women > 88 cm (35 in)
- Triglycerides ≥ 150 mg/dl
- HDL cholesterol: men < 40 mg/dl; women < 50 mg/dl
- Blood pressure ≥ 130/≥ 85 mmHg
- Fasting glucose ≥ 110 mg/dl

Diagnosis of metabolic syndrome is made when 3 or more of the risk determinants shown above are present.

There is an increasing evidence that insulin resistance is the fundamental defect linking individual components of metabolic syndrome, although the strength of association of insulin resistance to these components is variable in different populations and even within populations[8]. Insulin resistance will lead either to type 2 diabetes and subsequent CHD, or, if insulin secretion is maintained, to the development of metabolic syndrome without diabetes, and, again, to greatly increased risk of CHD[2].

The clinical manifestations of metabolic syndrome vary in different populations. Caucasians mainly show dyslipidaemia, African populations show hypertension, Native Americans show hyperglycaemia, and South Asians show both hyperglycaemia and accelerated CHD[2].

The ATP III criteria seem to be user-friendly in the diagnosis of metabolic syndrome in an out-patient setting. Only, approximately 50% patients with essential hypertension are insulin resitant/hyperinsulinaemic[2]. Similarly, not all

overweight subjects are insulin resistant as only about 25% of obese individuals could be classified as being insulin-resistant[9].

The ATP III criteria most likely to identify resitant/hyperinsulinaemic individuals are the changes in plasma triglyceride (TG) and HDL cholesterol (HDL-C) concentrations. The TG/HDL-C concentration ratio is comparable to fasting plasma insulin concentration as an indicator of insulin resistance[9]. In addition, this ratio provides an independent estimate of CHD risk. This means that if in an individual with essential hypertension, the TG/HDL-C concentration ratio is low; he does not have insulin resistance and, so, is not at increased risk of CHD.

AETIOPATHOGENESIS

Most of the parts of the world have shown a renaissance from persistent famine stricken days to availability of abundant high fat and calories diet. At the same time, life styles of the people have become sedentary mostly in the rapidly developing industrialized world.

Our bodies, which until now have been programmed to adapt to under nutrition by virtue of permanent metabolic and endocrine changes, are unable to handle this deluge of food supply, and this results in obesity[10]. It has been already pointed out that insulin resistance which is the main cause of metabolic syndrome is directly related to obesity. Excess fat, as long as it is inside adipocytes, does not cause deleterious effect on health[2]. Over the past years, adipose tissue has been recognized as a major site for steroid hormone metabolism[11] and for the production of leptin, adiponectin, resistin, pro-inflammatory cytokines, compliment factors and other molecules, collectively called adipocytokines. These adipose tissue-secreted proteins are essential components of the physiological system that integrate endocrine, autocrine and paracrine signals to mediate multiple processes including insulin sensitivity, energy metabolism, blood coagulation and inflammatory responses[12]. Because many cytokines, such as tumour necrosis factor TNF-α, interleukin (IL)-6 and IL-1α, are secreted by adipose tissue, increasing levels of obesity are often associated with increased concentrations of these pro-inflammatory cytokines. Chronic low-grade inflammation is undoubtedly a component of the metabolic syndrome but the mechanisms linking insulin resistance and inflammation are uncertain[12, 13]. Studies done on animal models of obesity show that leptin causes fat to deposit primarily in adipocytes[2]. Leptin deficiency or resistance leads to tissue deposition of fat[2]. This ectopic distribution of fat (triglycerides) particularly its visceral or central component, causes insulin resistance[14]. It seems leptin causes tolerance for fat as insulin causes tolerance for glucose and leptin deficiency or resistance may be a more central cause of insulin resistance and eventual development of metabolic syndrome[2].

Genetic factors play an important role in human fat distribution and are responsible for 70% of the variation in intra-abdominal fat mass[14]. The other important determinant is sex, with males being typified by central and females by peripheral fat distribution[14].

There is a strong evidence to suggest that excess FFA is the cause for insulin resistance[15, 16]. There is intracellular accumulation of triglycerides, and, probably more importantly, of intracellular fatty acid metabolites (fatty acid CoA's, diacylglycerol, and ceramides) in the insulinresponsive tissues, which interfere with upstream insulin signaling events resulting in acquired insulin signaling defects[17]. In skeletal muscle, it leads to impaired glucose transporter (GLUT 4) translocation to the cell membrane and results in resistance to insulin stimulated glucose uptake[17]. In liver, there is resistance to insulin-mediated suppression of hepatic glucose production[15]. Increased plasma FFA level leads to impaired insulin secretion by β cells probably via increased intracellular expression of uncoupling protein 215. Thus, insulin resistance in metabolic syndrome is post-receptor in origin.

Hypertension in metabolic syndrome may be caused by several mechanisms. Leptin may increase blood pressure by causing sympathetic activation[2]. Endothelial dysfunction manifests as blunting of the biologic effect of a potent endothelium-derived vasodilator, nitric oxide, and increased production of vasoconstrictors such as angiotensin II, endothelin-1, and cyclooxygenase and lipooxygenase products of arachidonic acid metabolism, seems to be the most important mechanism[18]. Other mechanism involved may be renal sodium retention secondary to hyperinsulinaemia[18].

METABOLIC SYNDROME – IS IT CURABLE?

The current modalities of treatment of metabolic syndrome include diet, exercise and pharmacotherapy. Yet, metabolic syndrome remains a clinical dilemma with relentless progression and far-reaching implications. Unfortunately, the etiology of this condition is still elusive and conventional therapeutic modalities cannot achieve a cure. This knowledge is now being challenged by a growing body of evidence that remission of diabetes, that is, long term restoration of normal glycemia and glycated haemoglobin levels without medications, can often be achieved after bariatric surgery. Return to euglycaemia and normal insulin levels are observed within days after surgery, suggesting that weight loss alone cannot entirely explain why surgery improves diabetes[19, 20].

Although, at present there are no specific guidelines for the management of metabolic syndrome, it seems the key to success lies in life-style modification that promotes weight reduction by increasing physical activity and decreasing the amount of saturated fat in diet[21].

Life-style Modifications

The current generation consumes maximum junk food stuffs right from the school days with minimum physical exercise and sedentary life style. On top of this, most of our leisure hours are spent watching television or playing computer games and there are almost non-existent physical education programmes in our schools or work places.

The health benefits of regular physical activity as a primary preventive measure is beyond doubt, and physicians have a crucial role in passing this information to their patients particularly those who are overweight and with a sedentary lifestyle, when counseling them about life-style changes[22].

Regular exercise improves insulin sensitivity, decreases plasma triglyceride levels, and reduces cardiovascular morbidity and mortality[23]. The activity should be in the form of aerobic exercise of moderate intensity like riding a bicycle, jogging, taking a brisk walk, and gardening, raking leaves, or even playing actively with kids[24]. Accumulating at least 30 minutes of daily physical activity is enough to help reduce and maintain body weight. For weight reduction, reduction in daily fat intake is essential. Saturated fat (mainly dairy and animal fat) worsens insulin resistance and increases LDL cholesterol level[25]. Therefore, their daily intake should be restricted to 7-10% of caloric intake[25]. Dietary cholesterol should be restricted to less than 200 mg/day[25]. Incorporation of monounsaturated fatty acid (fat from plant source like olive oil, soybean oil, canola oil, safflower oil, peanut oil, peanuts, peanut butter, almond, and cashew nut) may be beneficial as it improves the atherogenic dyslipidaemia[25]. Similarly, n-3 polyunsaturated fatty acids (mainly from fish) have cardioprotective effect. Polyunsaturated fatty acid should constitute approximately 10% of energy intake[25]. Viscous (soluble) fibre (mainly in oat products, psyllium and pectin) intake of 10-25 g/day also improves atherogenic dyslipidaemia[25]. A diet incorporating whole grain cereals, fruits, vegetables, nut, legumes and low fat milk is rich in all these ingredients[25, 26].

Structured programmes that emphasise life-style changes, including education, reduced fat (< 30% of daily energy) intake, regular physical activity, and regular participant

contact, have the potential to produce long-term weight loss.

Is There a Role Of Antioxidants?

It was seen that mega doses of dietary antioxidants – vitamin C, vitamin E, selenium, beta-carotene, and other carotenoids – have not demonstrated protection against cardiovascular disease or diabetes[27]. Large placebo-controlled trials have failed to show benefit and, in some instances, have suggested adverse effects of antioxidant vitamins[27].

Smoking increases the risk of CVD events and should be strongly discouraged.

Pharmacological Therapy

Although, at present, pharmacological treatment is not recommended to tackle the insulin resistance of metabolic syndrome, every opportunity should be taken to treat patients with type 2 diabetes and metabolic syndrome with the insulin sensitisers – metformin and thiazolidinediones[28]. Thiazolidinediones appear to act by lowering FFA levels.

Like fibrates, they lower triglyceride level and raise HDL cholesterol level. There is also evidence for role of acarbose in the prevention of glucose toxicity and beta-cell exhaustion and it should be an essential component of any anti-diabetic regimen in patients with type 2 diabetes and metabolic syndrome[29].

ACE-inhibitor ramipril in the HOPE trial has indisputably demonstrated reduction and/or prevention of cardiovascular events in a broad range of high-risk patients with preserved LV function[30]. Ramipril should be a first choice antihypertensive agent in an individual with hypertension associated with metabolic syndrome. Ramipril is thought to reduce cardiovascular morbidity and mortality by slowing the progression of atherosclerotic plaque formation, preserving endothelial function, and reducing plaque activation independently of effects on blood pressure and lipid levels. It is interesting to note that ramipril also prevented the development of type 2 diabetes in the study participants probably by reducing insulin resistance[30].

Although statins only partially correct the atherogenic dyslipidaemia, lowering of LDL cholesterol remains the first target. There is evidence that statins may reduce new onset diabetes and may therefore be beneficial for individuals with metabolic syndrome[2].

Surgical Cure For Diabetes Mellitus And Metabolic Syndrome!

The recent upsurge of Bariatric surgical procedures could be the answer to this intriguing problem. Using surgery explicitly to treat metabolic disorders including diabetes is a revolutionary concept and represents a disruption to current therapeutic paradigms[31]. The exact mechanism for the dramatic effect of surgical procedures for obesity on metabolic syndrome remains unknown. A meta-analysis involving 136 studies for a total of 22,094 patients showed that type 2 diabetes was completely resolved in 76.8% and improved in 86.0% of patients who had undergone bariatric surgery[32].

What makes bariatric surgery so effective in controlling diabetes? Various hypotheses have been proposed. Amongst all, the hind gut hypothesis involving the entero-insular axis is more acceptable[33]. It has been documented that:

- Bariatric Surgery improves insulin sensitivity
- Resolution of diabetes occurs even before weight loss occurs
- Weight loss and intake reduction do not appear to be the key mechanism[32.]

Altogether various studies show that gastrointestinal bypass operations can achieve control of diabetes by mechanisms that are independent of the treatment of obesity and surgically induced weight loss[33, 34].

CONCLUSION

Obesity is a complex multifactorial disease affecting over 300 million people worldwide, and is associated with increased morbidity

and mortality. The alarming increases in obesity especially its central component resulting in metabolic syndrome, seems to be behind the twin epidemic of type 2 diabetes and cardiovascular disease currently sweeping the Indian subcontinent. Sedentary life-style and easy-availability of energy-dense food are the driving force for this growing menace. Community based programmes to promote healthy living are needed to tackle this crisis.

Controlled trials in centers with a wide experience of bariatric surgery are needed to verify the possibility of a surgical cure specific to the problem. Surgeries for obesity seem to have a potential for changing the current concepts of the pathophysiology of the metabolic syndrome and, possibly, the management of the disease.

REFERENCES

1. Wild SH, Byrne CD. The global burden of the Metabolic Syndrome and its consequences for diabetes and cardiovascular disease. In: Byrne CD, Wild SM (eds), The Metabolic Syndrome. England, John Wiley & Sons (Asia) PTe Ltd, 2006,pp.1-32.
2. Bloom garden ZT, Obesity, hypertension and insulin resistance. Diabetes Care, 25: 2088-97, (2002).
3. Reaven G, Banting Lecture: Role of Insulin resistance in human disease. Diabetes, 37: 1595-1607, (1988).
4. Wild SH, Roglic G, Greeb A, et al., Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care, 27:1047, (2004).
5. Misra A, Vikram NK, Insulin resistance syndrome (metabolic syndrome) and obesity in Asian Indians: evidence and implications. Nutrition, 20:482, (2004).
6. Neel JV, Diabetes mellitus: A 'thrifty' genotype rendered detrimental by 'progress'. Am J Hum Genet, 14:353, (1962).
7. Executive summary of the third report of the national cholesterol education program (NECP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA, 285:2847-97, (2001).
8. World Health Organizaton: Report of a WHO consultation: definition of metabolic syndrome in definition, diagnosis and classification of diabetes and its complications. Diagnosis and classification of diabetes mellitus, Geneva, Word Health Organization, Department of Noncommunicable Disease Surveillance, 1999.
9. Reaven G. Metabolic syndrome: pathophysiology and implications for management of cardiovascular disease. Circulation. 107: 287-8, (2002).
10. Bjorntorp P.Thrifty genes and human obesity. Are we chasing ghosts? Lancet. 358: 1007-8, (2001).
11. Stulnig TM, Waldhaust W. 11β-hydroxylsteroid dehydrogenase type 1 in obesity and Type 2 diabetes. Diabetologia. 47:1, (2004).
12. Flier JS. The adipocyte: Storage depot on the energy information superhighway? Cell. 80:15, (1995).
13. Tilg H, Moshen AR. Adipocytokines: Mediators linking adipose tissue, inflammation and immunity. Nat Rev immunol. 6:772, (2006).
14. Montague CT, O'Rahilly S. The perils of portliness: Causes and consequences of visceral obesity. Diabetes. 49: 883-8, (2000).
15. Sheehan MT, Jensen MD. Metabolic complications of obesity: Pathophysiologic considerations. Med Clin N Am. 84: 373-85, (2000).
16. Langin D. Diabetes, insulin secretion, and the pancreatic beta-cell

mitochondrion. N Eng J Med. 345: 1772-4, (2001).
17. Shulman GI. Cellular mechanisms of insulin resistance. J Clin Invest. 107: 171-7, (2000).
18. Taylor AA. Pathophysiology of hypertension and endothelial dysfunction in patients with diabetes mellitus. Endocrinol and Metab Clinics of N Am. 30:983-97, (2001).
19. Hanley AJG, Festa A, D' Agostino RB, et al. Metabolic and inflammation variable clusters and prediction of type 2 diabetes . Diabetes. 53: 1773, (2004).
20. Greenway SE, Greenway F, Klein S. Effects of obesity surgery on noninsulin-dependent diabetes mellitus. Arch Surg. 137:1109, (2002).
21. Bloom garden ZT. Obesity and diabetes. Diabetes Care. 23: 1584-90, (2000).
22. Noel PH, Pugh JA. Clinical review: Management of overweight and obese adults. BMJ. 325:757-71, (2002).
23. Koplan JP, Dietz WH. Caloric imbalance and public health policy. JAMA. 282: 1579-81, (1999).
24. Hwang MY, Glass RM, Molter J. Are you obese? JAMA. 282: 1597, (1999).
25. American Diabetes Association. Evidence based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. Diabetes Care. 25: S50-S70, (2002).
26. Hwang MY, Glass RM, Molter J. Why you should eat more fruits and vegetables. JAMA. 282: 1304, (1999).
27. Lonn E. Do antioxidant vitamins protect against atherosclerosis? The proof is still lacking. J Am Coll Cardiol. 38: 1795-7, (2001).
28. Bloom garten ZT. Thiazolidinediones, obesity and related topics. Diabetes Care. 24: 172-7, (2001).
29. Chiasson JL, Josse RG, Gomis R, et al. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomized trial. Lancet. 359: 2072-7, (2002).
30. Kennedy J, Mogensen CE, Ball SG, et al. What is the relevance of the HOPE study in general practice? IJCP. 55: 449-57, (2001).
31. Chowbey P. Metabolic Syndrome-Surgical management. In: R L Gupta (eds.), Recent advances in Surgery, Jaypee Brothers Medical Publishers (P) Ltd, India, 2009, pp.133-147.
32. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: A systematic review and meta-analysis. JAMA. 292:1724, (2004).
33. Patriti A, Facchiano E, Sanna A, et al. The enteroinsular axis and the recovery from type 2 diabetes after bariatric surgery. Obes surg. 14:840, (2004).
34. Cohen RV, Schiavon CA, Pinheiro JS, et al. Duodenal-jejunal bypass for the treatment of type-2 diabetes in patients with BMI 22-34: a report of two cases. Surg Obes Relat Dis. 3:195, (2007).