

25 The Metabolic Syndrome— Health and Economic Impact: Indian Scene

Abstract: The 'metabolic syndrome' or 'insulin resistance syndrome' was originally described by Reaven in 1988 as Syndrome X. This syndrome accommodates the clustering together of certain cardiovascular risk factors associated with insulin resistance and hyperinsulinemia.

The metabolic syndrome has been defined differently by various agencies and the cut-off points for some of the parameters vary according to various regions of the world. The guidelines as applicable to the Indians are given in this article. The importance of easily measurable clinical parameters like abdominal obesity has been shown to be sine quanon of metabolic syndrome and the projected figures of diabetes, cardiovascular disease and rising incidence of metabolic syndrome have been emphasized.

The effort has been made to calculate the economic burden of treating such a large number of patients. The emphasis on modifying the lifestyle factors in preventing the clustering of risk factors of metabolic syndrome, diabetes and cardiovascular disease has been highlighted.

DEFINITION

The 'metabolic syndrome' or 'insulin resistance syndrome' was originally described by Reaven in 1988 as Syndrome X. This syndrome accommodates the clustering together of certain cardiovascular risk factors associated with insulin resistance and hyperinsulinaemia.

The metabolic syndrome as defined by the World Health Organization (WHO)¹ and ATP III definitions of the syndrome,² while similar, are not identical. The two definitions are summarized in Table 1. The Indian criteria for diagnosis of metabolic syndrome is given in Table 2.³

While the insulin resistance syndrome has worn many previous labels over the past three decades, metabolic syndrome gained pre-eminence after publication and revision of the World Health Organization's Expert Committee Report on the diagnosis and classification of diabetes mellitus in 1999, and the National Cholesterol Education Program (NCEP), Adult Treatment Panel-III (ATP III) guidelines in the USA in 2001. While the definitions provided by these two working groups present some differences, both predict a significantly greater risk of developing diabetes in those not yet afflicted as well as an excess of coronary heart disease and total cardiovascular disease. The syndrome is poised to become pandemic as the worldwide race to obesity runs unchecked in a global population that is aging.

ASSOCIATED RISK FACTORS

In addition to the clinical criteria used to define the metabolic syndrome, the syndrome is associated with postprandial hyperinsulinemia and resistance to insulin's glucose and fatty acid-lowering actions, greater density and numbers of low-density lipoprotein (LDL) - cholesterol particles, decreased levels of the cardioprotective high-density lipoprotein (HDL) - cholesterol,

and skewing of the residual HDL particles toward smaller and less beneficial fractions. Obesity and the metabolic syndrome are also linked with high levels of inflammatory risk markers/factors, such as interleukins, tumor necrosis factor α (TNF α), and C-reactive protein (CRP), and defects in fibrinolysis, such as elevated plasminogen activator inhibitor-1 (PAI 1) and a greater magnitude of oxidative stress.

The risk of obesity, hypertension, diabetes and an excess of cardiovascular and renal diseases, were well described 80 years ago.⁴ Subsequent studies showed that obesity, especially when linked with a truncal or abdominal fat distribution is associated with hypertension, faster heart rates, hyperinsulinemia, and insulin resistance with related abnormalities of carbohydrate and lipid metabolism. Thus, the quartet of diabetes, hypertension, dyslipidemia and obesity also called lifestyle diseases are considered as cardiovascular risk factors for the metabolic syndrome⁵ (Fig. 1). These diseases together have a tremendous impact on Health Economics in India by causing cardiovascular involvement.

Obesity

The International Obesity Task Force estimates that more than 300 million individuals worldwide are obese and an additional 800 million are overweight.⁶ For the first time, the number of overweight individuals in the world is equivalent to the number of underweight. Unless current trends are reversed, the health-related and economic consequences will be enormous. Successful maintenance of the lifestyle changes needed for optimum bodyweight, although possible in some individuals, is uncommon and the current methods for lifestyle modification (alone) as a treatment for obesity are widely regarded as ineffective.

Table 2: Indian criteria for diagnosis of the metabolic syndrome (Joshi, JAPI)

<i>Abdominal Obesity Waist Circumference</i>	
Men	>35 inch (>90 cm)
Women	>27 inch (>68.5 cm)
Triglycerides	>150 mg/dl
HDL-Cholesterol	
Men	<35 mg/dl
Women	<38 mg/dl
Blood Pressure	>130/>85 mm Hg
Fasting Glucose	>110 mg/dl

HDL, high-density lipoprotein

Antiobesity pharmacotherapy is a potentially important adjunctive treatment to lifestyle modification. The ideal antiobesity drug has three characteristics. First, it should cause sustained clinically significant reductions in bodyweight and reduce obesity-related morbidity and mortality. Second, the benefit-risk ratio of the drug must be favorable. The track record for safety of antiobesity drugs has been particularly poor, whereas their potential for abuse by non-obese individuals striving to lose weight is high. Third, future affordability and availability are important considerations because obesity is a condition that disproportionately affects minorities and those of low socioeconomic status. The cost of pharmacotherapy would be Rs. 2,000 - Rs. 3,500 per year depending on the agent used. Lifestyle modification still remains⁵ the cornerstone of treatment.

DIABETES

The spreading diabetes epidemic is a major health threat for India and threatens to bankrupt our nation. The unprecedented increase in diabetes prevalence is evident from the report of World

Health Organization (WHO), which shows that India tops the world with the largest number of diabetic subjects. According to recent WHO estimates, presently, India has 32 million diabetic subjects and this is projected to increase to 100 million, i.e. rise by 250% by the year 2035. This means by that time India will contribute to more than one-fifth - 20% of the total diabetic population in the world. Further support for the rising prevalence comes from the major studies from west and south India. The study reported from western India of 10 cities (Mumbai, Thane, Pune, Nasik, New Mumbai, Raigad, Surat, Vapi, Ahmedabad, Baroda) shows that every fifth Mumbaikar will have Diabetes.⁷ Similar data is seen in south India by Mohan, et al in his Chennai Urban Population Study (CUPS) and Chennai Urban Rural Epidemiology Study (CURES) of the Madras Diabetes Research Foundation and MV Diabetes Specialities Centre, Chennai and his colleagues.⁸ In the CUPS study, 12% of individuals above the age of 20 years in Chennai were found to be diabetic in the year 1997. In the more recent CURES study, conducted on 26001 individuals showed that 16% now have diabetes in Chennai. Dr. Mohan's comparative studies on migrant Indians and Europeans conducted in UK in the 1980's showed, that 10% of Asian Indian diabetics in the UK had both parents diabetic, compared to only 1% of European diabetics suggesting that the inheritance is stronger among Indians.⁹ The CUPS study also showed that nearly 60% of the offspring of two diabetic parents had either diabetes or pre-diabetes in Chennai.

Urbanization has led to rapid changes in life style, with more white-collar jobs leading to decreased physical activity and affluence associated with consumption of fast foods rich in fat, sugar and calories. This epidemiological transition has led to a paradigm shift in the health patterns in the country, from communicable disease to non-communicable diseases such as diabetes. This study also revealed that as obesity, particularly abdominal obesity, increased the prevalence of diabetes soared.⁹

India is expected to lose \$237 billion in national income due to chronic non-communicable diseases (CNCs), according to the World Health Organization (WHO). It is thus imperative that the country recognizes the threat of CNCs, say experts in a paper published in the journal Nature. CNCs include cardiovascular disease (mainly heart disease and stroke), chronic respiratory diseases, some cancers and Type 2 diabetes. These are responsible for 60% of deaths worldwide with 80% occurring in low and middle-income countries. It is very much the (developing) countries, struggling to create a healthcare system, which are now being hit by the double burden of disease: both infectious diseases and these chronic diseases. The economic burden of diabetes is substantial, as it currently accounts for an average of around 8% of total health care budgets in developed countries.

The primary cost of diabetes treatment for medications only, vary from Rs. 800 to Rs. 5000 per patient per year depending on the type of oral hypoglycemic agent used. From Rs. 4500 to Rs. 14,000 per year depending on the type of insulin and insulin devices used. In Type 1 diabetic patients, considering the cost of meters and monitoring strips, the outgoing would be Rs. 5,000 per year if monitored weekly.

Table 3: Studies on prevalence of hypertension in rural Indian population

Author	Place	Year	Age group (Years)	Hypertension criteria (mm Hg)	Prevalence	
					Men % Sample size	Women % Sample size
Gupta SP	Haryana	1977	20-69	>160/95	3.50 (154)	3.69 (891)
Wasir	Delhi	1983	>20	>160/95	3.20 (441)	7.50 (464)
Baldwa	Rajasthan	1984	21-60	>141/91	6.93 (447)	8.81 (465)
Puri	Himalayan Institute	1986	15-82	>160/95	2.44 (1592)	2.38 (1511)
Hussain	Rajasthan	1988	20-60	>160/95	5.72 (1328)	6.43 (1150)
Kumar	Rajasthan	1991	>21	>160/95	4.00 (3742)	3.60 (3098)
Joshi	Maharashtra	1993	>16	>160/95	4.85 (227)	3.17 (221)

Jajoo	Maharashtra	1993	>20	>160/95	2.89	(2247)	4.06	(1798)
Agarwal	Uttar Pradesh	1994	>20	>160/95	1.57	(3760)	-	-
Malhotra	Haryana	1999	16-70	>140/90	3.00	(2259)	5.80	-
Hazarika	Assam	2004	>30	JNC-VI	33.3	(3180)	-	-
Thankappan	Kerala	2006	>30	JNC-VII	36	(2159)	37.2	(2796)

A Type 2 diabetic patient without any complication will spend Rs. 6,200-10,700/- per year. Type 1 diabetic will have to spend Rs. 8,000-18,000/- per year. Cost of complication of diabetes would be more than cost of treating primary disease, i.e. diabetes. Thus effective management of diabetes is essential to avoid the economic burden of treating complications.

Table 4: Studies on prevalence of hypertension in urban Indian population

Author	Place	Year	Age group (Years)	Hypertension criteria (mm Hg)	Prevalence			
					Men % Sample size	Women % Sample size		
Mathur	Agra	1963	>20	>160/95	3.98	(1408)	6.64	(227)
Malhotra	Railway Hospital	1970	20-58	>160/95	6.2	(2638)	-	-
					15.2	(1594)		
Gupta SP	Rohtak	1978	>20	>160/95	6.00	(1151)	7.00	(872)
Dalal	Mumbai	1980	>18		15.63	(3148)	15.38	(2575)
Wasir	New Delhi	1984	20-60	160/95	3.80	(1767)	1.45	(688)
Ahmed	Karnataka	1988	>21	DBP>90	10.20	(698)	2.00	(102)
Hussain	Rajasthan	1988	20-60	>140/90	6.15	(1561)	7.33	(1103)
Chaddha	New Delhi	1990	25-64	>160/90	11.66	(637)	13.68	(7351)
Gupta R	Jaipur	1995	>20	>140/90	30.00	(1415)	34.00	(797)
Anand	Mumbai	2000	28-65	>140/90	26.78	(1512)	27.65	(141)
Shanthirani	Chennai	2003	>20	>140/90	22.8	(557)	19.7	(705)
Gupta R	Jaipur	2002	>20	>140/90	36.36	(550)	37.52	(573)
Bharucha	Mumbai	2004	>20	>140/90	32.8	(1099)	39.4	(1316)
Deepa	Chennai	2004	>20	>140/90	22.1	(262)	-	-
Ashavaid	Mumbai	2004	-	>140/90	22.5	(39940)	-	-

The cost of effective control of hypertension would involve using more than 2 antihypertensive agents. This would mean that on an average patient will have to spend Rs. 2,000-5,000/- per year depending on the type of drugs used.

HYPERTENSION

The incidence of hypertension is increasing over the years and as shown in Tables 3 and 4, the incidence is higher in urban than in rural Indians.¹⁰ In diabetics, the incidence of hypertension is more than 40%. As per UKPDS study it is easier to control and maintain blood pressure with antihypertensive agents than it is to control diabetes.¹¹

DYSLIPIDEMIA

In Type 2 diabetes there are both lipid and lipoprotein abnormalities. Central obesity, through its endocrine function and release of cytokines, initiates insulin resistance (IR) by increasing circulating nonesterified FFA muscle. In the adipocyte, insulin normally suppresses hormone sensitive lipase and postprandial lipolysis; however, in IR, there is an inappropriate release of FFAs after meals. Metabolic effect of elevated free fatty acids and central obesity is shown in Fig. 2.¹²

A variety of dyslipidemias and their management diabetic patients is shown in Table 5. The most common patterns are elevated triglycerides (TGs), low high-density lipoprotein (HDL) and small dense LDL. Elevated cholesterol with or without increased very low-density lipoprotein (VLDL) and TGs is common in diabetic patients with proteinuria, especially in cases

of massive proteinuria seen in diabetes-associated nephritic syndrome. Also seen in diabetic individuals with proteinuria is an elevated level of the atherogenic lipoprotein (a) [Lp (a)].¹³

Statins and Fibrates

Controlled clinical trials show greater cardiovascular benefits from statin therapy in patient subgroups with Type 2 diabetes, impaired fasting glucose and metabolic syndrome. According to the ATP III and ADA guidelines, statins are the first-line drugs for the treatment of dyslipidemia of diabetes.¹⁴ This class of drug is the most effective in reducing LDL-C; it lowers TGs (20-30%) and raises HDL-C moderately (5-10%). Statin-induced rise in HDL is thought to be caused by inhibiting the geranylgeranyl pyrophosphate (GGPP) pathway and prenylation of Rho proteins which indirectly lead to PPARα activation. Statin-induced reduction in plasma concentration of LDL and VLDL is due to enhanced clearance by the LDL receptor. Isolated hypertriglyceridemia is seen in a large population of Indian diabetic patients. Fibrates and niacin are recommended along with statins for management of hypertriglyceridemia.

Effective management of hyperlipidemia would cost Rs. 3,000 -Rs. 5,000/- per year, which is essential as various studies have shown that statins should be prescribed to every patient with metabolic syndrome to reduce the morbidity and mortality resulting from cardiovascular complications.

Hypertension, obesity and dyslipidemia along with diabetes will greatly increase the health care burden syndrome. Antioxidants are freely prescribed to diabetic patients for variety of reasons. This would add Rs. 1,000/- per patient per year to the treatment regimen. Also every patient of metabolic syndrome will need aspirin as a preventive therapy. The cost of therapy would go up by Rs. 1,000/- every year.

Table 5: Dyslipidemia in adults

LDL-C lowering

First choice: HMG-CoA reductase inhibitor (statin)

Second choice : Fibrates or ezetimibe (used with statin)

HDL-C lowering

Behavior intervention such as weight loss, increased physical activity, and smoking cessation

Glycemic control

Nicotinic acid (most effective agent), fibrates

TG lowering

Glycemic control first priority

Fibrates, fish oil, nicotin acid

Statins are moderately effective at high dose in hypertriglyceridemic subjects who also have high LDL-C

Polypill for Metabolic Syndrome: The SAMTA Pill

Wald and Law have produced a good paper on the classical 'Polypill' in BMJ. Modern Indian diet and lifestyle have increased the population levels of several of the causal "risk factors" and their combined effects have made the diseases common. Cardiovascular disease can be avoided or delayed, but the necessary changes to Modern Indian diet and lifestyle are not practicable in the short-term. Drug treatment to prevent IHD events and stroke has generally been limited to single risk factors, to targeting the minority of patients with values in the tail of the risk factor distribution, and to reducing the risk factors to "average" population values. This policy can achieve only modest reductions in disease. Ward and Law described a strategy to prevent

cardiovascular disease based on these three principles and quantify the overall preventive effect.¹⁵ They show that a daily treatment with the Polypill, comprising six components, each lowering one of the above four risk factors, would prevent more than 80% of IHD events and strokes, with a low risk of adverse effects. This strategy would be suitable for people with known cardiovascular disease and for everyone over a specified age (say 55), without requiring risk factors to be measured.

There is now considerable evidence to show that Statins, Aspirin, Metformin and antihypertensive agents such as Thiazides and ACE inhibitors (or Angiotensin receptor blocker) can reduce morbidity and mortality due to cardiovascular disease. It could theoretically at least suggest that many patients with Type 2 diabetes would benefit from the SAMTA combination of therapies. Varadhan et al have called this the SAMTA pill because Indo-linguistically SAMTA means equality and SAMTA pill may be a method of equalizing the increased cardiovascular morbidity and mortality in diabetes to that of the nondiabetic population.¹⁶ The SAMTA pill offers the prospect of considerable reduction in cardiovascular morbidity and mortality in a primary prevention cohort of patients with Type 2 diabetes. The close correlation of actual Steno-2 and Polypill-predicted event rates may offer a 'Proof of Concept' for the Polypill. The Polypill or 'Aspostatinoprilololazide folate' may offer a realistic opportunity to reduce cardiovascular complications in patients with Type 2 diabetes.

Health Impact

The combined cost of treating hypertension, diabetes, obesity and dyslipidemia would work out to Rs. 15,700/- Rs. 28,200/- per year, not considering the complications of these diseases. Considering the per capita income of \$ 1,000 (Rs. 40,000/-) per year, it would be necessary for government/NGO and individuals initiatives to quell the health impact of this syndrome in Indian scenario. Only future will tell whether an ideal Polypill will solve the health and economic impact of metabolic syndrome in Indian Scene.

Also, greater awareness of these non-communicable diseases and early intervention with lifestyle modifications including diet and regular exercise will reduce the economic burden on individuals as well as the nation.

CONCLUSION

Cardiovascular disease is the leading cause of death and disability. Metabolic syndrome adds to the morbidity and mortality of cardiovascular disease. Considering the cost of treating the quartet of metabolic syndrome and its complications and going into the past of health economics of the country preventive strategies of early detections and measures for tight control instituted early in the disease is recommended. Also, development of an ideal Polypill to treat the syndrome is the need of the hour.

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