**Alpha Blockers and Metabolic Syndrome**

Nitin K Kabra *

**Introduction**

Metabolic syndrome is a constellation of cardiovascular risk factors in one individual that predicts an approximately 3-fold increased risk for new onset type 2 diabetes and a 2-fold increased risk of cardiovascular events.

Different definitions of metabolic syndrome have been proposed by different organisations (see table) but systemic hypertension and central obesity remain common to all.

Metabolic syndrome is highly prevalent in patients with hypertension. In a population-based study (the SMOOTH study) involving 4,590 consecutive subjects attending the primary care service of 9 general practitioners, the overall prevalence of metabolic syndrome was 13.4%, being much higher in hypertensive than in normotensive subjects (24 versus 4%, P < 0.0001).1

Sympathetic nervous system plays an important role in the initiation and maintenance of elevated blood pressure in essential hypertension (Figure 1).2,3 Data collected in experimental animal models of hypertension as well as in human hypertension provide conclusive evidence that alterations in the sympathetic control of heart rate, cardiac output, peripheral vascular resistance and renal sodium handling may promote alone or in combination, the development and progression of the hypertensive state.2,3 Subjects with metabolic syndrome display greater levels of sympathetic nerve traffic.4,5 When obesity and hypertension are concomitantly present in the same patient, the degree of sympathetic activation is much greater than in patients with either condition singly.6

In the metabolic syndrome, as in other cardiovascular diseases, sympathetic overactivity has an adverse impact on both cardiovascular function and

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<tr>
<td>Insulin resistance (T2DM / IGT / IFG), plus 2 of the following:</td>
<td>• Abdominal obesity: WHR &gt; 0.9 in men or &gt; 0.85 in women, or BMI &gt; 30 kg/m²</td>
<td>• Waist circumference &gt; 102 cm in men, &gt; 88 cm in women</td>
<td>• Waist circumference ≥ 94 cm in men, ≥ 80 cm in women</td>
<td>• Any 3 (or more) of the following:</td>
<td>• Central obesity (ethnicity-specific values; can be assumed if BMI &gt; 30 kg/m²), plus 2 of the following:</td>
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<td>• TG ≥ 150 mg/dl, and/or HDL-C &lt; 40 mg/dl in men, &lt; 50 mg/dl in women</td>
<td>• TG ≥ 150 mg/dl and/or HDL-C &lt; 39 mg/dl in men or women</td>
<td>• TG ≥ 150 mg/dl</td>
<td>• HDL-C &lt; 40 mg/dl in men, &lt; 50 mg/dl in women</td>
<td>• Waist circumference &gt; 102 cm in men, &gt; 88 cm in women</td>
<td>• TG ≥ 150 mg/dl</td>
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<td>• BP ≥ 140/90 mmHg</td>
<td>• BP ≥ 140/90 mmHg or taking antihypertensive drugs</td>
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<td>• BP ≥ 130/85 mmHg</td>
<td>• Fasting glucose ≥ 110 mg/dl</td>
<td>• HDL-C &lt; 40 mg/dl in men, &lt; 50 mg/dl in women</td>
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<td>• Microalbuminuria: urinary albumin secretion rate ≥ 20 μg/min, or albumin-to-creatinine ratio ≥ 30 mg/g</td>
<td>• Fasting glucose ≥ 110 mg/dl</td>
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<td>• BP ≥ 130/85 mmHg</td>
<td>• In 2003, ADA modified the criteria for IFG tolerance, to 100 mg/dl from 110 mg/dl</td>
<td>• Fasting glucose ≥ 100 mg/dl</td>
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*Professor and HOD, Department of Cardiology, Gandhi Medical College / Hospital, Secunderabad
cardiovascular prognosis. A state of adrenergic overdrive carries an adverse impact on cardiovascular morbidity and mortality, thus representing an important clinical and therapeutic target.

Demonstration by Smithwick that surgical resection of thoracolumbar sympathetic chain resulted in lowering of elevated blood pressure, provided a rationale for the use of drugs which lower blood pressure by decreasing sympathetic tone by blocking sympathetic neurotransmission at different levels. These include:

- Ganglion blockers which are obsolete now,
- Centrally acting alpha-2 adrenoceptor antagonists which are in limited use, and
- Beta adrenoceptor antagonists which are widely used.
- Alpha-adrenoceptor antagonists – selective and nonselective.

Non-selective alpha-adrenoceptor antagonists: e.g. Phenoxybenzamine, phentolamine, are effective in lowering blood pressure but no longer used in the treatment of essential hypertension because of unacceptable side effects such as tachycardia and rapid development of tolerance. Their clinical use is limited to preoperative treatment of phaeochromocytoma, and as a pharmacologic diagnostic test of this tumour.

Selective alpha-1 adrenoceptor antagonists: e.g. Prazosin, Doxazosin, Terazosin.

Selective post junctional alpha adrenergic inhibition with high selectivity for alpha-1 receptors. Have extremely low affinity for alpha-2 receptor. Decrease blood pressure by reducing peripheral vascular resistance, thus reversing the fundamental haemodynamic abnormality of hypertension. They cause only a modest reflex tachycardia and a degree of vasodilatation, both on the arterial and venous sides of the circulation, contributes to the maintenance of an adequate cardiac output, protection against exercise-induced rises in blood pressure and better exercise capacity than in patient treated with beta-blockers. Renal blood flow and GFR are well maintained during long term treatment with prazosin and clinically they appear to preserve renal function.

All alpha blockers produce consistently significant reductions in both systolic and diastolic blood pressures following long term therapy. The blood pressure reduction with prazosin in various studies have ranged from 7-34 mmHg. for diastolic blood pressure and 10-52 mmHg. for systolic blood pressure. The antihypertensive efficacy of these agents is similar in elderly and younger patients. The efficacy of selective alpha-blockers is comparable with that of the other antihypertensive drugs when evaluated in comparable patients in controlled trials.

Alpha antagonists could have some advantages over “conventional” first-line treatment.

Effects on Cardiovascular Risk Factors

Management of overall cardiovascular risk is an important goal of antihypertensive treatment. The favourable effects of alpha 1 adrenoceptor antagonists both on serum insulin and on cholesterol and triglyceride levels have led to suggestions that these drugs may have a role in the treatment of diabetic hypertension.

Effects on plasma lipids

Lipid lowering effect of alpha blockers has been documented in several studies but the magnitude of fall in LDL cholesterol and rise in HDL cholesterol is modest.

It can modify plasma levels of atherogenic lipids by several mechanisms which include:
1. Inhibition of absorption of dietary cholesterol.
2. Changes in the metabolism of triglyceride - rich lipoproteins.
3. Reduction in hepatic cholesterol synthesis.
4. Stimulation of lipoprotein cholesterol synthesis.
5. Reduction in VLDL secretion rate.
6. Up-regulation of LDL receptors.
7. Diversion of fatty acid metabolism to oxidation rather than triglyceride synthesis.
8. May also influence blood flow to sites of lipoprotein synthesis and catabolism.

In a large observational study of 13,381 hypertensive patients treated with prazosin GITS formulation for 14 weeks showed a significant reduction in total cholesterol (237.7 mg/dl - 228.5 mg/dl; p< 0.0001), HDL-cholesterol (58.5 mg/dl-60 mg/dl; p< 0.0001),
Triglycerides 152.3 mg/dl-141mg/dl; p< 0.0001) and Glucose levels in the blood (104.8 mg/dl-103.5 mg/dl; p< 0.0001).

Cox et.al in a pooling of results of 13 double blind placebo-controlled studies using Doxazosin found a mean reduction in triglycerides of 9.1% and increase in HDL cholesterol of 7.6%.14

Effects on Insulin and Glucose

Some epidemiological studies have shown a highly significant association between hypertension and glucose intolerance, insulin resistance and /or hyperinsulinaemia.15 Prazosin treatment has been shown to increase insulin sensitivity.16

In Type II hypertensive diabetics, Doxazosin, but not captopril or nifedipine, improved glucose tolerance, free fatty acid concentrations, insulin-mediated glucose uptake, glucose oxidation and non oxidative glucose disposal.17

In head-to-head comparisons with other drugs, Doxazosin increased insulin sensitivity while enalapril, an angiotensin-converting enzyme (ACE) inhibitor18 or irbesartan, angiotensin II receptor blocker19 had no metabolic impact.

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Alpha blockers in metabolic syndrome

Hypertension complicated by multiple metabolic alterations is frequent in the general population and is often associated with increased cardio-vascular risk, particularly if it coexists with diabetes and abdominal adiposity.15 In recent years, the relationships among sympathetic dysfunction, metabolic syndrome and cardiovascular risk have engendered much interest. As a result, sympathetic over activity is increasingly being considered a major target for therapeutic interventions aimed at reducing global cardiovascular risk and it should also be one of the goals of pharmacological interventions employed in the metabolic syndrome, and particularly of antihypertensive drug treatment.20

Doxazosin improved endothelial-mediated vasomotor function and reversed abnormal arteriolar structure in hypertensive patients with metabolic syndrome while improving lipid profile and blunting post-glucose hyperinsulinaemia.21 In experimental animals, Doxazosin decreased TNF-α production,22 a key factor in the genesis of insulin resistance in MS.23 Doxazosin, but not amlodipine, also reduced mean platelet volume, a marker of abnormal platelet activation and a correlate of insulin resistance in hypertensive patients with MS.24 α-1 blocking drugs also seem to decrease fasting and post-meal free fatty acids25 to protect from the adverse impact of salt restriction on serum lipids and insulin sensitivity.26 This observation is relevant because diuretics or severe salt restriction can boost sympathetic activity and, therefore, aggravate insulin resistance.27 In insulin-resistant, hyperinsulinemic nondiabetic hypertensive patients with chronic renal failure, 12-month Doxazosin treatment was associated with reduction of the HOMA index and fasting plasma insulin levels, while no effect was found in response to amlodipine.

In British South Asians, an ethnic group at high coronary risk with strong predisposition to Type II diabetes, insulin resistance and MS, Doxazosin reduced glucose, total and LDL cholesterol, triglycerides, and increased HDL cholesterol. Doxazosin treatment lowered plasma insulin levels and increased tissue plasminogen activator (t-PA) mass. Bendrofluazide, a thiazide diuretic, showed the opposite metabolic effects.28

Conclusions

Alpha,β-blockers may be an attractive therapeutic option in general practice because there are no absolute contraindications to their use. Therefore, there is little concern about underlying conditions or common concomitant diseases. Alpha-adrenoceptor antagonists can frequently be used where other classes of antihypertensive drugs are contraindicated; example in bronchial asthma and conduction blocks. In severe hypertension these agents may be successfully used in drugs combination with any of the other classes of drugs, including calcium antagonists and ACE inhibitors.29

At present no specific guidelines for the treatment of the metabolic syndrome are available, sympathoinhibition appears to be a key goal of the therapeutic approach to the metabolic syndrome.

The beneficial effects of alpha-adrenoceptor antagonists on endothelial function, lipid parameters, glucose homoeostasis and insulin sensitivity may be the most important in hypertensive patients with metabolic syndrome but whether or not are they predictive of clinical outcomes with respect to cardiovascular mortality needs to be tested in appropriately designed clinical trials.

References


