The treatment of hypertension in the metabolic syndrome

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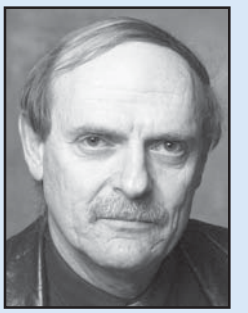

Introduction

The metabolic syndrome, previously known as the 'deadly quartet', 'syndrome X' or the 'insulin resistance syndrome', can be defined as the occurrence of insulin resistance, obesity (upper body or abdominal), dyslipidaemia and hypertension in an individual.[1] It leads to a markedly increased risk of cardiovascular disease and non-insulin dependent (type 2) diabetes mellitus.[2,3]

Although recognised for nearly 20 years, precise definitions have only recently been described by the World Health Organisation (WHO) and the National Cholesterol Education Programme (NCEP).[4,5] These definitions have been validated by Laaksonen et al.[6] where the WHO definition was found to be highly sensitive and specific in predicting diabetes mellitus whereas the NCEP definition identified those at a high risk of developing diabetes, but was relatively insensitive in predicting diabetes. This disorder is common, with a recent study demonstrating an age-adjusted prevalence of 23.7% in the USA[7] whereas a further study in Finland noted a prevalence of 8.8–14.3%.[8] Although the prevalence is similar for men and women, the latter have a higher cardiovascular risk than men.[9]

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The underlying abnormality is insulin resistance with elevation of serum triglycerides and decreased high density lipoprotein (HDL) cholesterol. Hyperglycaemia may be present. In addition, other disorders such as hyperuricaemia, disorders of coagulation and endothelial function have also been described.[3] The pathogenesis of the disorder is not clearly defined, but it is thought that genetic, dietary and environmental factors play a role.[10] Manipulation of the latter two factors may alter the poor outcomes of this disorder.

Antihypertensive treatment

Hypertension is thought to be due to the interaction between insulin and its counterregularity hormones (catecholamines, glucocorticoids, glucagon) and free fatty acids. It is associated with increased cardiovascular tone, elevated resting heart rate and decreased heart-rate variability.[11] Treatment can be either non-pharmacological or pharmacological.

Non-pharmacological treatment

One may predict that sustained weight loss and correction of the lipid abnormalities may result in a reversal of the syndrome with a decrease in blood pressure. A number of studies have been performed, both in animals and man, in an attempt to cause weight loss and assess the consequences of such a manoeuvre. In an elegant study performed in rats, it was found that altering the rats' diet from a high fat and high refined carbohydrate diet which had resulted in obesity, hypertension, hyperinsulinaemia and

hypertriglyceridaemia to a low fat, high complex carbohydrate diet resulted in normalisation of glucose transport, blood pressure, plasma insulin and very low density lipoprotein cholesterol with a decrease in obesity.[12] This particular study had been performed over a two-year period and whether such an effect could also be produced in man is another matter, as laboratory-based rats have no choice but to comply with their diet.

There is, however, evidence that the metabolic syndrome can be reversed in man. Shahid et al.[13] noted that an exercise programme could decrease plasma triglycerides, decrease systolic blood pressure and increase insulin sensitivity. In the second study, manipulation of diet and an exercise programme has been shown to markedly decrease the incidence of diabetes mellitus in a group (522 individuals) of middle-aged, overweight people with impaired glucose tolerance.[14] Therefore, dietary manipulation and physical activity should be first line therapy and remain core treatment for individuals with this syndrome. However, many patients have difficulty remaining compliant to regular exercise and dietary restriction for lengthy periods of time. For these individuals, and in those where diet and exercise has proved insufficient to control blood pressure, pharmacological antihypertensive therapy is required.

The best advice for those patients with a metabolic syndrome who require pharmacological management for hypertension would be to lose weight and to exercise

Pharmacological treatment

The groups of anti-hypertensive agents and their metabolic effects are shown in the table.

Theoretically, knowing the metabolic and cardiovascular effects of the different anti-hypertensives should allow the prescriber to predict which would be the most suitable agent for patients with a metabolic syndrome. Furthermore, one may expect that randomised controlled trials would have been performed demonstrating superiority for one or more group of drugs in preventing the cardiovascular sequelae of this syndrome. No such studies have been performed and the prescriber has to dredge the large anti-hypertensive drug study literature to compare varying regimes. Assuming equal blood pressure lowering efficacy, one would assume that those drugs with no or only minor

Table 1. Effects of obesity and antihypertensives on metabolic parameters found in the metabolic syndrome

Condition/Drug	Lipids	Blood Glucose	Uric Acid
Obesity	↑ triglycerides ↓ HDL	↑ or N	N
ACE inhibitors	N	↓ or N	N
Alpha blockers	N or ↑ HDL	N	N
Beta blockers	↑ triglycerides [23] ↓ HDL cholesterol[23]	↑ or N [22]	N
Calcium Channel blockers	N	↑ or N	N
Thiazide duretics [a]	Short term ↑ triglycerides [23] ↑ LDL chol Long term N [23]	↑ or N [22]	↑

KEY

↑ = increase; ↓ = decrease; N = neutral

ACE = angiotension – converting – enzyme

[a] = Effects on triglycerides, blood glucose and uric acid are dose dependent, usually minimal at doses equivalent to 2.5mg bendrofluazide

[22/23] = See references

metabolic changes would be superior to other agents. This would suggest that angiotensin converting enzyme inhibitors (ACE inhibitors), alpha blockers or calcium channel blockers (CCB) would be the most suitable, but this may not be the case. The recent ALLHAT trial comparing chlorthalidone (similar to a thiazide diuretic), doxazosin (alpha receptor blocker), lisinopril (ACE inhibitor) and amlodipine (CCB) was unable to show that chlorthalidone was inferior to the other agents in decreasing the incidence of coronary heart disease (CHD) or other cardiovascular disease (CVD) in hypertensive patients who had at least one other CHD risk.[15] Indeed, the doxazosin arm of the trial had to be terminated early because of excess CVD morbidity and mortality when compared to chlorthalidone.[16] Chlorthalidone was superior to both lisinopril and amlodipine in decreasing the risk of development of heart failure over time.[15] In general, it was superior to lisinopril in decreasing the risk of other CVD manifestations. These results were found despite the findings that the diuretic increased fasting blood glucose in comparison to other agents. All three drugs were associated with a decrease in serum cholesterol, but lisinopril and amlodipine were superior to chlorthalidone in this regard.[15]

Overall, no clinical trial has shown major differences in preventing CVD/CHD complications in patients with hypertension between the major drug groups independent of other risk factors.[17–21]

Conclusion

The best advice for those patients with a metabolic syndrome who require pharmacological management for hypertension would be to lose weight and to exercise. Unless contraindicated (patients with gout) a thiazide diuretic should be the drug of first choice. If this is inadequate or the patient has had an overt episode of coronary heart disease, then perhaps a beta blocker should be added. Otherwise, any member of the above drug groups should be used. Alpha blockers should probably be used as third line treatment only.

References

1. Nambi V, Hoogwerf B, Sprecher D. A truly deadly quartet: obesity, hypertension, hypertriglyceridemia, and hyperinsulinemia. Cleve Clin J Med 2002; 69:985-9.
2. Sprecher D, Pearce G. How deadly is the 'deadly quartet'? A post CABG evaluation. J Am Coll Cardiol 2000; 36:1159-65.
3. Liese A, Mayer-Davis E, Haffner S. Development of the multiple metabolic syndrome: An epidemiological perspective. Epidemiol Rev 1998; 20:157–72.
4. Alberti K, Zimmet P. Definition, diagnosis and classification of diabetes mellitus and its complications,1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998; 15:539–53.
5. Executive summary of the 3rd report of the National Cholesterol Education Programme (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001; 285:2486–97.
6. Laaksonen D, Lakka H-M, Niskanen L et al. Metabolic syndrome and development of diabetes mellitus: Application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. Am J Epidemiol 2002; 156:1070–7.
7. Ford E, Giles W, Dietz W. Prevalence of the metabolic syndrome among US adults. JAMA 2002; 287:356–9.
8. Lakka H-M, Laaksonen D, Lakka T et al. The metabolic syndrome and total and cardiovascular disease mortality in middle aged men. JAMA 2002; 288:2709–16.
9. Wilson P, Kannel W, Silbershatz H et al. Clustering of metabolic factors and coronary heart disease. ARCH Intern Med 1999; 159:1104–9.
10. Bouchard C. Genetics and the metabolic syndrome. Int J Obes Relat Metab Disord 1995; 19 (Suppl 1): S52–9.
11. Brotman D, Girod J. The metabolic syndrome: A tug-of-war with no winner. Cleve Clin J. 2002; 69:990–4.
12. Roberts C, Vaziri N, Hui Liang K et al. Reversibility of chronic experimental syndrome X by diet modification. Hypertension 2001; 37:1323–28.
13. Shahid S, Schneider S. Effects of exercise on insulin resistance syndrome. Coron Artery Dis 2000; 11:103–9.
14. Tuomilehto J, Linstrom J, Eriksson J et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001; 344:1343–50.
15. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomised to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002; 288:2981–97.
16. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomised to doxazonsin vs chlorthalidone: the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2000; 283:1967–75.
17. Hansson L, Lindholm L, Ekbom T et al. Randomised trial of old and new antihypertensive drugs in elderly patients: Cardiovascular mortality and morbidity. The Swedish Trial in Old Patients with Hypertension-2 Study. Lancet 1999; 354:1751–6.
18. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatments in older persons with isolated systolic hypertension. JAMA 1991; 265: 3255-64.
19. Psaty B, Smith N, Siscovick D, et al. Health outcomes associated with antihypertensive therapies used as first-line agents: A systematic review and meta-analysis. JAMA 1997; 277:739–45.
20. Staessen J, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension: This systolic hypertension in Europe (SYST-EUR) Trial Investigators. Lancet 1997; 350:757–64.
21. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor ramipril, on cardiovascular events in high-risk patients: the heart outcomes prevention evaluation study investigators. N Engl J Med 2000; 342:145–53.
22. Luna B, Feinglos M. Drug-induced hyperglycemia. JAMA 2001; 286:194–8.
23. Stone N. Secondary causes of hyperlipidaemia. Med Clin North America 1994; 78:117–41.