CURRENT OPINION

Drugs 2004; 64 (8): 795-803
0012-6667/04/0008-0795/$34.00/0

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The Management of Hypertension in the Overweight and Obese Patient

Is Weight Reduction Sufficient?

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Abstract

The management of hypertension in the overweight and obese patient is a frequently encountered but under investigated clinical problem. The conventional management of such patients involves weight reduction with dietary therapy or a combined approach with dietary and anti-obesity drug therapy. However, long-term weight reduction, which is necessary to sustain blood pressure (BP) control, is not feasible in over 80% of patients.

Anti-obesity therapy with orlistat has inconsistent effects on BP and may benefit only patients who have uncontrolled or non-medicated hypertension. Anti-obesity therapy with sibutramine may be associated with a modest worsening of BP control. Consequently, antihypertensive drug therapy is often required to supplement a weight reduction programme, and also in patients with severe hypertension or hypertension-associated end-organ damage.

Treatment with a thiazide diuretic should be considered as first-line antihypertensive drug therapy in overweight and obese patients. ACE inhibitors or non-dihydropyridine calcium channel antagonists are reasonable alternatives where clinically indicated, or they can be used in combination with a thiazide diuretic if treatment with the diuretic alone is insufficient. If such treatment is inadequate for BP control, the addition or substitution of an α- or β-adrenoceptor antagonist may be considered, although the latter can be associated with weight gain. Concurrent disease is an important determinant of first-line and supplementary antihypertensive drug therapy.

Additional studies are needed to determine the long-term (>1 year) efficacy and safety of antihypertensive and anti-obesity management strategies in the overweight and obese hypertensive patient.

Hypertension occurs in about 60% of patients who are overweight (body mass index [BMI]: 25–29.9 kg/m^2) or obese (BMI: ≥30 kg/m^2).[1] The mechanisms of obesity-related hypertension are not clear, but include sodium and fluid retention, insulin resistance, adipocyte-mediated effects on angiotensin II and atrial natriuretic peptide levels, and leptin-mediated enhancement of sympathetic activity.[2] Despite the considerable scope of this clinical problem, there are few guidelines regarding the management of the overweight and obese hypertensive patient. Most clinical guidelines, such as those of the World Health Organization International Society for Hypertension,[3] emphasise the need for weight loss as an initial intervention to control and prevent hypertension. Several authorities advocate

weight loss of 5–10% of baseline weight to control blood pressure (BP), reduce antihypertensive drug therapy needs and to improve other cardiovascular risk factors.[4-6] However, few studies have critically assessed the evidence relating to the efficacy and safety of weight loss interventions to control BP in the overweight or obese hypertensive patient.[7,8]

Therefore, we undertook a systematic review to identify clinical trials that investigated the efficacy of weight loss on BP control in overweight and obese hypertensive patients. The objective of this review is to determine the efficacy of three strategies for BP control: (i) dietary and lifestyle changes; (ii) anti-obesity drug therapy; and (iii) antihypertensive drug therapy.

1. Data Sources

The Medline (1993 to April 2003), HealthSTAR (1993 to April 2003) and Cochrane Controlled Trials Register (1993 to April 2003) databases were searched for contemporary weight reduction studies in overweight or obese adults, aged 18–65 years. The search strategy used the key words: 'obesity', 'overweight', 'hypertension', 'body mass index', 'treatment', 'weight reduction', 'randomised controlled trial' and 'clinical trial'. Eligible studies satisfied five criteria: (i) the study assessed patients with treated or untreated hypertension or high to normal BP; (ii) the study was a prospective clinical trial; (iii) the study population consisted of overweight or obese adults with a BMI ≥25 kg/m^2; (iv) the study investigated a nonpharmacological or pharmacological antihypertensive intervention; and (v) the duration of the intervention (and patient follow-up) was at least 1 year. The later criterion was adopted because obesity and hypertension are considered chronic diseases,[9,10] in which the potential benefits of interventions aimed at BP reduction need to be assessed over the long term.

2. Dietary and Lifestyle Modification

Four randomised, controlled trials have investigated the efficacy of dietary therapy on BP control in overweight and obese hypertensive patients.

The first study, the Trial of Hypertension Prevention (phase II),[11,12] compared weight loss alone, dietary sodium restriction, combined weight loss and sodium restriction, and usual care in 2382 overweight or obese individuals who had non-medicated high to normal BP (systolic BP [SBP] <140mm Hg, diastolic BP [DBP] 83–89mm Hg). In this study, in which patients underwent 2 years of follow up, mean weight loss in patients who received weight loss, dietary sodium restriction, combined weight loss and sodium restriction, and usual care was −2.0, +0.4, −2.2 and +0.7kg, respectively. Weight reduction was associated with modest, but statistically significant, reductions in SBP (−3.2mm Hg) compared with usual care. Dietary sodium restriction was associated with a statistically significant reduction in SBP (−3.0mm Hg), whereas combined weight reduction and sodium restriction offered no advantage over either intervention alone. A noteworthy finding was that patients with a sustained weight loss of ≥4.5kg after 3 years had a 65% lower risk of developing hypertension (hazard ratio [HR] = 0.35; 95% CI 0.20, 0.59). However, such patients comprised only 13% of study participants.

The second study investigated reduced dietary sodium intake, weight loss, combined dietary sodium restriction and weight loss, or usual care in 585 elderly obese hypertensive patients (average SBP <145mm Hg, DBP <85mm Hg while receiving a single antihypertensive medication).[13] Withdrawal of antihypertensive medication was attempted after 3 months. After 29 months, there was an approximately 40–50% lower risk for the composite outcome of new-onset hypertension, antihypertensive therapy and a cardiovascular event with reduced sodium intake (HR = 0.60; 95% CI 0.45, 0.80), weight loss (HR = 0.64; 95% CI 0.49, 0.85) and combined reduced sodium intake-weight loss (HR = 0.47; 95% CI 0.35, 0.64). The average reduction in weight for the study participants assigned to a weight loss group was approximately 3.5–4.5kg.

The third study investigated if obese patients with medicated hypertension could discontinue treatment and remain normotensive with dietary therapy alone.[14] Patients were randomly allocated

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to receive a nutritional intervention, consisting of weight loss and reduced sodium and alcohol intake, and withdrawal of antihypertensive therapy (group 1), withdrawal of antihypertensive therapy without the nutritional intervention (group 2) or continued antihypertensive therapy without the nutritional intervention (group 3). After 4 years, there was 1.8kg weight loss in group 1 and 2kg weight gain in groups 2 and 3 ($p < 0.001$). Although SBP and DBP increased in all groups, 39% of group 1 patients remained normotensive without drug therapy compared with 5% of group 2 patients ($p < 0.001$).

Finally, the fourth study compared the efficacy of a pre-packaged meal plan with usual care in 302 obese, hypertensive patients who also had hyperlipidaemia or type 2 diabetes mellitus.[15] After 1 year, there was a significantly improved metabolic profile, including a significant reduction in SBP, with the dietary intervention. The dietary intervention was associated with a mean weight loss of approximately 6kg in the hyperlipidaemic group and approximately 3kg in the diabetic group.

Overall, dietary interventions that are associated with modest (≤5kg) weight loss may confer benefits to control BP and reduce antihypertensive drug therapy requirements in overweight and obese patients with hypertension. However, these benefits appear to be contingent on sustained weight loss, which may be feasible in only a small proportion of such patients.

3. Anti-obesity Drug Therapy

There are two anti-obesity drugs, orlistat and sibutramine, currently approved by the US FDA. At present, orlistat is approved for use for not more than 2 years, whereas sibutramine is approved for use for not more than 1 year. This issue is relevant because the safety of long-term (>2 years) use of orlistat and sibutramine has not been established. Other weight-loss drug treatments, such as benzfetamine and phentermine, are approved only for short-term use of 3 months or less.

3.1 Orlistat

Five randomised, placebo-controlled trials have investigated the antihypertensive effect of orlistat, a gastrointestinal lipase inhibitor that reduces fat absorption by about 30%,[16] in mixed normotensive-hypertensive patients with type 2 diabetes mellitus or other cardiac risk factors.[17-21]

These studies consistently demonstrated that orlistat 120mg three times daily when combined with a dietary regimen, was more effective than diet only therapy for weight loss, with weight loss of 5–10kg after 1–2 years.[17-20] In three studies,[17-19] patients who received orlistat did not have statistically significant differences in SBP or DBP compared with those who received placebo, with differences in SBP and DBP of <2 and <1mm Hg, respectively, between the orlistat and placebo groups. However, another study involving obese and overweight patients with type 2 diabetes found that orlistat therapy was associated with a significant reduction in SBP in patients who received orlistat compared with placebo (−2.1 versus −0.3mm Hg; $p < 0.05$), although there were no data on DBP effects.[20] Furthermore, a study involving obese patients with inadequately controlled hypertension found that orlistat therapy was associated with a significant reduction in DBP (−11.4 versus −9.2mm Hg; $p < 0.01$), but there was no significant effect on SBP compared with dietary therapy alone (−13.3 versus −11.0mm Hg).[21]

Overall, although orlistat therapy consistently confers greater weight loss than dietary therapy alone, it has inconsistent effects on BP. These discrepant findings might be due to differences in baseline patient characteristics: a beneficial effect on BP with orlistat-associated weight loss may be more likely in patients with non-medicated or uncontrolled hypertension. In support of this contention, a meta-analysis of orlistat treatment studies of 1 year's duration investigated effects on BP in subgroups with hypertension and found that orlistat therapy conferred significantly greater reductions in SBP (9.4 versus 4.6mm Hg; $p = 0.022$) and DBP (7.7 versus 5.6mm Hg; $p = 0.017$) than placebo.[22]

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3.2 Sibutramine

Sibutramine, a serotonin and noradrenalin reuptake inhibitor that induces weight loss through enhanced satiety and increased basal energy expenditure,[23] may be considered in obese hypertensive patients with controlled hypertension. However, its use is contraindicated in patients with ischaemic heart disease and congestive heart failure, many of whom may be overweight or obese. Two randomised, placebo-controlled, 1-year trials have investigated the effects of sibutramine on BP in obese hypertensive patients.

The first study investigated sibutramine 20 mg/day therapy in 224 patients with medicated hypertension.[24] Although sibutramine therapy conferred greater weight loss than placebo (4.7 versus 0.7%; $p < 0.05$), its use was associated with a nonsignificant (1–2mm Hg) increase in SBP and DBP and a significant increase in heart rate (4.9 beats/minute) [$p < 0.05$].

The second study investigated sibutramine 20 mg/day therapy in 220 obese patients with hypertension well controlled by an ACE inhibitor with or without a diuretic.[25] Again, sibutramine therapy conferred greater weight loss than placebo (4.5 versus 0.4kg; $p < 0.05$), but sibutramine-treated patients had higher levels of SBP and DBP. Furthermore, patients' resting heart rate increased by 5.7 beats/minute with sibutramine therapy.

Overall, the weight loss effects of sibutramine therapy do not appear to translate into favourable effects on BP. Instead, sibutramine therapy may be associated with small increases in BP and resting heart rate.

4. Antihypertensive Drug Therapy in the Obese and Overweight Patient

In general, the efficacy of weight reduction for BP control in overweight and obese hypertensive patients may be limited over the long term because of weight loss recidivism that occurs in over 80% of such patients.[26] Consequently, antihypertensive drug therapy is often required to supplement a weight loss intervention for BP control. As outlined in table I, there are several antihypertensive drug classes that merit consideration because of different efficacy and safety profiles. Although few studies have investigated antihypertensive drug therapy in a strictly overweight and obese population, it is likely that the findings from unselected hypertensive patients are applicable to overweight and obese patients.

Table I. Antihypertensive drug therapy in the overweight and obese patient with hypertension

Antihypertensive drug class	Role in antihypertensive therapy	Comments
ACE inhibitors	Alternative first-line therapy with compelling indication (e.g. heart failure, diabetes mellitus, nephropathy)	No deleterious effects on glycaemic control or blood lipids Can be combined with thiazide diuretic
Calcium channel antagonists	Alternative first-line therapy with compelling indication (e.g. diabetes)	Non-dihydropyridine drugs (verapamil) preferable because of greater efficacy
		Can be combined with thiazide diuretic
Thiazide-type diuretics	First-line therapy	May require additional antihypertensive therapy
		Low-dose therapy preferred to minimise adverse effects
α-Adrenoceptor antagonists	Second-line therapy	Potential adverse effects in patients with congestive heart failure
		Potential positive effect on glycaemic control
β-Adrenoceptor antagonists	Second-line therapy	May be associated with 0.5–3.5kg weight gain
		Possible deleterious effects on glycaemic control and blood lipids avoided with combined thiazide diuretic
		Potential beneficial effects in heart failure and after myocardial infarction

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4.1 ACE Inhibitors

There are several potential benefits of ACE inhibitor therapy in the overweight and obese hypertensive patient. In general, ACE inhibitors are well tolerated and effective antihypertensive agents that have the potential to reduce ventricular hypertrophy, renal hyperfiltration and microalbuminuria, conditions that are common in overweight and obese patients.[27] ACE inhibitor therapy also improves insulin sensitivity and decreases the risk for type 2 diabetes, which is relevant because obese patients are prone to dysglycaemia.[28] Furthermore, ACE inhibitors do not have deleterious effects on lipids levels, which is another advantage because of the high prevalence of dyslipidaemia in obese patients.[29]

One clinical trial compared enalapril and amlodipine therapy in obese hypertensive patients who were also randomised to a weight loss programme or usual care.[30] After 1 year, there was no difference in weight loss in patients who received enalapril or amlodipine. However, enalapril-treated patients had lower catecholamine, insulin and leptin levels, thereby suggesting more favourable metabolic effects of ACE inhibitor-mediated BP control.

Based on these considerations, ACE inhibitors are a reasonable treatment option for the management of hypertension in overweight or obese patients. The effects of the newer class of angiotensin receptor antagonists, although not as widely investigated as ACE inhibitors, share some of the beneficial effects of ACE inhibitors and are likely also to be of benefit in overweight and obese hypertensive patients.

4.2 Calcium Channel Antagonists

Dihydropyridine calcium channel antagonists, such as amlodipine, nifedipine and isradipine, may have limited antihypertensive efficacy in overweight and obese hypertensive patients. These agents enhance natriuresis and decrease peripheral vascular resistance, the latter of which tends to be at lower baseline levels in obese compared with non-obese hypertensive patients. Consequently, the antihypertensive effects of such agents may be attenuated in obese patients. One study found that the antihypertensive response of nifedipine was negatively correlated as the level of adiposity increased.[31]

On the other hand, non-dihydropyridine calcium channel antagonists, such as verapamil, may be preferable in obese hypertensive patients because their antihypertensive effects are mediated primarily by negative chronotropic effects and have less peripheral vasodilating effects.[32] One non-randomised clinical trial found that long-acting verapamil therapy was efficacious and well tolerated in obese hypertensive patients.[33]

Thus, although, to our knowledge, there are no studies comparing different calcium channel antagonists in obese hypertensive patients, there is reasonable evidence to suggest that non-dihydropyridine agents are the preferred calcium channel antagonists in overweight and obese hypertensive patients.

4.3 Diuretics

Thiazide diuretics have comparable or superior antihypertensive efficacy to ACE inhibitors or calcium channel antagonists,[34] and are recommended as first-line drug therapy for uncomplicated hypertension by the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[35] Thiazide diuretics decrease intravascular volume and cardiac output and, therefore, may be of particular benefit in overweight and obese hypertensive patients in whom there is an increased likelihood of volume overload and increased cardiac output.[36] However, when high-dose diuretic regimens are used there is a concern about associated adverse metabolic effects that may be more pronounced in obese patients. Diuretics enhance sympathetic and renin-angiotensin activity and may have deleterious effects on glycaemic status and lipid levels.[37] However, with low-dose diuretic regimens, such as hydrochlorothiazide 12.5–25 mg/day, these adverse effects are minimised.[36]

If there is inadequate hypertensive control with low-dose diuretic therapy, the addition of another antihypertensive agent is preferable to increasing

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the diuretic dose. Consequently, combination therapy with a thiazide diuretic plus an ACE inhibitor or an angiotensin receptor antagonist are reasonable treatment options.

Overall, thiazide diuretics should be considered as first-line therapy in the overweight or obese hypertensive patient unless there is a compelling clinical indication to administer another class of antihypertensive drugs. However, diuretic therapy may require supplementation with an additional agent, such as an ACE inhibitor, a β-adrenoceptor antagonist or a calcium channel antagonist, to optimise antihypertensive efficacy.

4.4 α-Adrenoceptor Antagonists

α-Adrenoceptor antagonists, which include prazosin and doxazosin, have antihypertensive efficacy that is mediated through peripheral vasodilatory effects. These agents may be appealing for hypertensive patients with diabetes, many of whom are obese, because of associated improvements in glycaemic status.[38]

Few studies have investigated α-adrenoceptor antagonist use in obese hypertensive patients. One non-randomised clinical trial showed that prazosin was efficacious in controlling BP and also improved insulin sensitivity.[39] However, another study that compared the antihypertensive effects of doxazosin and chlortalidone found that doxazosin was associated with a 25% greater risk of adverse cardiovascular events, including a 2-fold greater risk of congestive heart failure.[40] Another clinical trial compared the response of six antihypertensive drugs of differing classes (hydrochlorothiazide, atenolol, captopril, clonidine, diltiazem, prazosin) in 1292 men, of whom 34% were obese.[41] In this study, prazosin had comparable antihypertensive efficacy to other options but was associated with an average weight gain of 1kg.

Overall, these agents may be less appealing in obese hypertensive patients with left ventricular dysfunction or congestive heart failure.

4.5 β-Adrenoceptor Antagonists

β-Adrenoceptor antagonists (β-blockers) are effective antihypertensive agents that reduce cardiac output through decreased sympathomimetic and renin-angiotensin activity. In overweight and obese hypertensive patients, β-blocker therapy may have potentially counteracting effects. On the one hand, these agents reduce left ventricular hypertrophy and heart failure, which are common in obese patients. On the other hand, β-blockers are associated with 0.5–3.5kg weight gain through decreased basal metabolic activity,[42] and may have deleterious effects on glucose[43] and lipid levels.[44] However, one large study found that β-blocker therapy (atenolol 25–100 mg/day) was superior to other antihypertensive drugs in controlling DBP in obese patients.[41]

Given these somewhat conflicting data, it may be reasonable to consider β-blocker therapy in obese hypertensive patients in whom the benefits are likely to outweigh the risks, such as those with a recent myocardial infarction or congestive cardiomyopathy.

5. Antihypertensive versus Dietary Therapy

There are few head-to-head clinical trials comparing antihypertensive drug therapy and weight reduction for BP control in overweight or obese hypertensive patients.

One small study randomly allocated 56 obese patients with mild hypertension, characterised by a DBP of 90–109mm Hg, to treatment with metoprolol 200 mg/day or a dietary regimen.[45] After 21 weeks, patients in the weight reduction group, who lost an average of 7.4kg, had a nonsignificantly greater reduction in SBP (13 versus 10mm Hg) and a statistically significant greater reduction in DBP (10 versus 6mm Hg) compared with the drug therapy group. Furthermore, patients in the metoprolol group had a worsened lipid profile, with a decrease in high density lipoprotein (HDL) cholesterol levels and an increased total cholesterol **:** HDL cholesterol ratio.

Another study randomly allocated 61 men, aged 40–69 years, with mild hypertension (DBP of

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90–104mm Hg) to dietary therapy or drug therapy with atenolol as first-line antihypertensive therapy, with additional drug therapy for BP control as required.[46] After 1 year, mean bodyweight decreased by 7.6kg in the diet group compared with a weight gain of 0.9kg in the drug therapy group. However, patients in the drug therapy group had significantly greater reductions in SBP (16 versus 4mm Hg; p = 0.003) and DBP (11 versus 3mm Hg; p = 0.002).

Overall, given this limited and conflicting data, further study is needed to assess the comparative efficacy of antihypertensive versus dietary therapy for BP control in overweight/obese patients.

6. Limitations of this Review and Existing Literature

Despite the fact that the management of the overweight and obese hypertensive patient is a frequently encountered clinical problem, few studies have investigated this issue directly and most available data are derived from studies that involved heterogeneous hypertensive patients, some of whom were overweight and obese. Therefore, additional studies are needed to: (i) compare different antihypertensive regimens; (ii) compare antihypertensive and anti-obesity weight reduction therapy; and (iii) determine the long-term (>1 year) efficacy and safety of different antihypertensive and anti-obesity management approaches.

Although weight reduction therapy appears to control BP, and would be preferable to antihypertensive drug therapy, this efficacy appears to be contingent on sustained weight loss, which may not be feasible in over 80% of people.[26]

7. Conclusions and Suggested Clinical Management

On the basis of the available data, the following guidelines can be considered as a basis for managing the overweight and obese hypertensive patient.

First, weight reduction, with dietary only or combined dietary-pharmacological therapy, remains the cornerstone of treatment in the overweight and obese hypertensive patient. This produces direct effects on BP and important effects on other metabolic parameters, such as control of blood glucose and lipids, which are woven in the pathophysiology of obesity-related cardiovascular disease. However, sustained weight reduction for more than 1–2 years has not been widely investigated and weight loss recidivism is common. Furthermore, anti-obesity drug therapy is not currently approved for use for longer than 1–2 years. Consequently, antihypertensive drug therapy may be often required to supplement weight loss interventions.

Secondly, if weight reduction therapy is inadequate for optimal BP control, if there is moderate-to-severe hypertension (SBP ≥140mm Hg; DBP ≥90mm Hg) or hypertension-associated end-organ damage, the use of antihypertensive drug therapy is warranted. First-line treatment in patients with uncomplicated hypertension should be with a thiazide diuretic. An ACE inhibitor or calcium channel antagonist are reasonable alternatives as first-line therapy in patients in whom there is a compelling clinical indication for such treatment. In patients in whom antihypertensive monotherapy is inadequate or in whom there is severe hypertension (i.e. SBP ≥160mm Hg, DBP ≥100mm Hg), a thiazide diuretic can be combined with either an ACE inhibitor or a calcium channel antagonist.

Thirdly, since comorbid conditions such as diabetes or coronary artery disease are common in the obese hypertensive patient,[47] the overall cardiovascular disease profile of patients should determine antihypertensive drug therapy (table I), as in the non-obese patient.[35]

Acknowledgements

No sources of funding were used to assist in the preparation of this manuscript. Dr Douketis is a recipient of a research scholarship from the Heart and Stroke Foundation of Canada and Dr Sharma is a Canada Research Chair for Cardiovascular Obesity Research and Management. Drs Douketis and Sharma have served as consultants and have received honoraria from manufacturers of anti-obesity drugs.

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