# The Challenge of Managing Hypertension in Patients with Diabetes or Other Endocrine Disorders

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## Abstract

Arterial hypertension is a frequent condition in the general population, but its prevalence increases in association with several endocrine diseases. Up to three-quarters of patients with diabetes are also hypertensive, and this association poses specific problems in the management of both conditions. Hypertension is a relevant condition in several other endocrinopathies and in some cases it is the main reason prompting patients to seek medical advice. Some of these endocrine diseases are frequent (primary aldosteronism) or may produce major complications (pheochromocytoma), and in any case require specific diagnostic work-ups and treatment.

## Keywords

Arterial hypertension, diabetes, endocrine diseases, primary aldosteronism, pheochromocytoma, Cushing's syndrome, endocrine hypertension

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## Hypertension and Diabetes

### The Size of the Problem

Arterial hypertension and diabetes are chronic pathological conditions presenting with a very high frequency in the adult general population. Hypertension affects about one-third of the adult population in developed countries,[1] with some variation between different countries and a relatively higher percentage in Europe compared with North America.[2] Large national differences also exist in prevalence rates for diabetes in Europe, ranging from 2.1 % in Iceland to 12.0 % in Germany; the number of adults with diabetes in the European countries is about 55 million, accounting for 8.5 % of the adult population in 2010.[3] Of note, the prevalence of hypertension in subjects with diabetes is much higher than in the general population: it has been estimated that up to 70–80 % of adults with diabetes present with blood pressure values ≥140/90 mmHg. This means that approximately 5 % of the adult population suffers from both diseases.

### Pathogenic Clues

There are several possible explanations for the unexpectedly high frequency of such co-morbidity. The progressive vascular damage seen in chronic hyperglycemia is associated with the development of earlier and more severe atherosclerosis, with accelerated age-related arterial stiffening, and increased systolic hypertension, as well as with microvascular damage, particularly in the kidney. Furthermore, hyperglycemia and/or the hyperinsulinemic state of type 2 diabetes may be responsible for sodium retention and volume expansion, thus increasing sodium sensitivity and blood pressure. On the other hand, it has also been proposed that hypertension-associated factors, such as increased sympathetic and/or renin–angiotensin activity, may favor the development of insulin resistance by limiting the access of insulin and glucose to skeletal muscle, the primary site of insulin-mediated glucose uptake. However, the association of hypertension and diabetes may reflect the existence of common underlying mechanism(s), either genetic or environmental. In this respect, obesity and insulin resistance are the two most relevant factors, often clustered in the so-called metabolic syndrome.

Over the last few years, obesity has reached epidemic proportions: more than 1 billion adults are currently overweight and at least 300 million of them are clinically obese. By 2030, the respective number of overweight and obese adults is projected to be 1.35 billion and 573 million individuals (or even 2.16 billion overweight and 1.12 billion obese individuals, if recent secular trends continue unabated).[4] In parallel, the total number of people with diabetes is projected to rise to 366 million in 2030. A new term has been coined to describe the incoming healthcare crisis: the diabesity epidemic.[5]

### Associated Risk and Benefit of Treatment

Regardless of the pathophysiological aspects, there is clear evidence that the association of hypertension and diabetes considerably increases cardiovascular risk, as pointed out in the Multiple Risk Factors Intervention Trial.[6] In this trial, at any given level of systolic

blood pressure, the absolute risk of cardiovascular death was approximately three-fold higher in subjects with type 2 diabetes compared with those without diabetes. Conversely, it has been unequivocally proved that blood pressure reduction is particularly important in patients with diabetes both to prevent cardiovascular disease and to minimize progression of renal disease and diabetic retinopathy. Evidence of benefit from treating hypertension in type 2 diabetes has come from several trials,[7–9] and the advantages of tight blood pressure control may be as great or even greater than the advantage of strict glycemic control.[9]

### When to Start Treatment and to what Extent to Reduce Blood Pressure

Given the serious negative effects of this co-morbidity, the first mandatory step is its detection; in other words every hypertensive or diabetic patient should have a careful assessment of his or her glycemic or blood pressure status, respectively. A second aspect of crucial relevance, sometimes unduly overlooked, is the enforcement of non-pharmacologic interventions in these patients. In fact, given the high prevalence of overweight/obesity in diabetic hypertensives, bodyweight reduction and increased physical activity may consistently improve both blood pressure and glycemic control.[10]

According to the 2007 guidelines for the management of arterial hypertension from the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC)[11] and the recent re-appraisal by an ESH Task Force,[12] the initiation of pharmacologic treatment is always indicated when blood pressure is ≥140/90 mmHg. It can also be suggested for subjects with diabetes who are in the high–normal blood pressure range (130/85–139/89 mmHg), particularly when microalbuminuria is present, although current evidence from trials does not strongly support this recommendation. The ESH/ESC 2007 guidelines indicated that the target blood pressure in patients with diabetes should be less than 130/80 mmHg;[11] however, a recent critical revision of the available evidence recognizes that this recommendation is not only unsupported by outcome evidence from trials, but also very difficult to achieve in most hypertensive diabetics. Consequently, it seems reasonable to pursue 'tight' blood pressure control[7] without indicating an overly ambitious and scientifically unproven goal.

### Which Drug(s) to Use

Treatment with all major antihypertensive drug classes—diuretics, beta-blockers, calcium channel antagonists, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor type 1 antagonists (ARBs)—is effective in reducing cardiovascular complications in diabetic hypertensives, emphasizing the protective effect of blood pressure lowering *per se*.[11,12] There is no compelling evidence of superiority of any single drug (or class); however, available data suggest that inhibition of the renin–angiotensin system (RAS), either with ACE inhibitors or ARBs, may offer some advantage, particularly against initiation or progression of nephropathy. It has also been proposed that inhibition of angiotensin II production or activity may improve glucose metabolism by increasing insulin sensitivity and/or protecting the pancreas via increased blood flow.[13,14] A few trials have directly evaluated the effect of pharmacologic treatment on the risk of new-onset diabetes and their results overall suggest a relatively weak protective effect of ACE inhibitors or ARBs compared with lifestyle intervention or other effective medications in the prevention of diabetes. In any case, a single drug is rarely sufficient to adequately control blood pressure in diabetic hypertensives; association therapy is usually necessary, and ESH/ESC guidelines suggest that a RAS inhibitor should always be part of antihypertensive drug treatment in these patients.[12]

**Figure 1: Suggested Work-up for the Management of Primary Aldosteronism[17]**


## Endocrine Hypertension

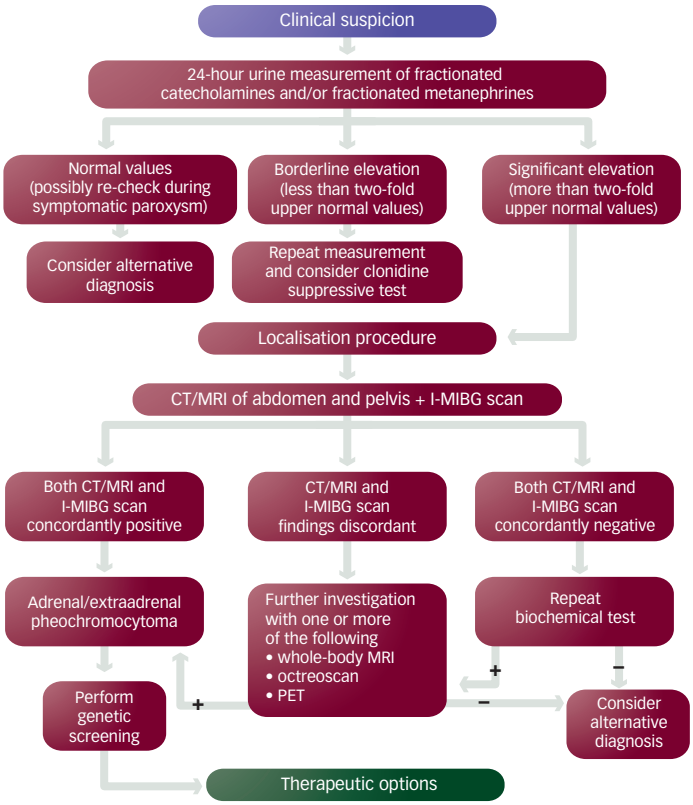
There are several endocrine diseases that are associated with the development of high blood pressure. Sometimes, arterial hypertension is the condition prompting the patient to seek medical advice, and it is very important to always take into account these forms of secondary hypertension in the diagnostic work-up.

### Primary Aldosteronism

The most frequent condition is certainly primary aldosteronism; its prevalence varies according to the criteria adopted for diagnosis (up to 10 % of the general hypertensive population). High blood pressure is almost invariably part of the syndrome[15] and in many cases high-grade (2 and 3) and/or resistant hypertension (defined as failure to achieve goal blood pressure despite adherence to an appropriate three-drug regimen including a diuretic) is present.

The elevation in blood pressure is dependent on mild volume expansion and an increase in systemic vascular resistance in the presence of excess mineralocorticoid activity.

**Figure 2: Diagnostic Flowchart for Suspected Pheochromocytoma[20]**




*CT = computed tomography; I-MIBG = $^{123}$I-metaiodobenzylguanidine; MRI = magnetic resonance imaging; PET = positron emission tomography.*

The first step for the diagnosis of primary aldosteronism is measurement of the aldosterone:renin ratio, followed by a confirmatory biochemical test (oral sodium loading, saline infusion, fludrocortisone suppression, or captopril challenge; see *Figure 1*).[16,17] When unregulated aldosterone hypersecretion is demonstrated, imaging and adrenal vein sampling techniques are indicated to identify the underlying cause. The key point is to differentiate pathological conditions that may benefit from surgical intervention (unilateral adrenal adenoma or, rarely, hyperplasia) from conditions (such as bilateral adrenal hyperplasia and/or adenomas) that require only appropriate medical treatment (including aldosterone receptor antagonists). Current guidelines emphasize the role of adrenal vein sampling as the reference standard test to differentiate unilateral from bilateral disease. The sensitivity and specificity of this technique (95 and 100 %, respectively) for detecting unilateral aldosterone hyperincretion are superior to those of adrenal computed tomography (CT: 78 and 75 %, respectively); moreover, CT can often be misleading by showing unilateral masses (with a consequent indication for surgery) where actually bilateral disease is present.

Blood pressure and serum potassium concentrations improve in nearly all patients with unilateral primary aldosteronism after laparoscopic adrenalectomy, and complete normalisation of blood pressure in the absence of antihypertensive drug treatment is achieved in about 50 % of patients.

In patients who do not undergo surgery and in those presenting bilateral adrenal disease, medical treatment is indicated. Mineralocorticoid receptor (MR) antagonists appear to be effective at controlling blood pressure and protecting against target organ damage. Among the MR antagonists, spironolactone has been considered the agent of choice; where available, canrenone (an active metabolite of spironolactone) or potassium canrenoate might be considered because they possibly have fewer sex-steroid-related side effects. A small dose of a thiazide diuretic, triamterene, or amiloride can be added to reduce the dose of spironolactone and the related side effects. Eplerenone, a newer, selective MR antagonist devoid of antiandrogen and progesterone agonist effects, might also be considered, although its better tolerability profile is counterbalanced by higher cost, multiple daily dosing and lack of clinical trial evidence for its use in primary aldosteronism. Other classes of antihypertensive drugs (calcium channel blockers, ACE inhibitors, and ARBs) can obviously be added to achieve adequate blood pressure control, and aldosterone synthase inhibitors may play a role in the future.

## Cushing's Syndrome

The incidence of Cushing's syndrome (excluding those cases caused by exogenous steroid or adrenocorticotrophic hormone [ACTH] administration) ranges from 0.7 to 2.4 per million population per year. However, new data suggest that Cushing's syndrome is more common than previously thought. In obese patients with type 2 diabetes, especially those with poor blood glucose control and hypertension, the reported prevalence of Cushing's syndrome is between 2 and 5 %. High blood pressure, mostly moderate diastolic hypertension, is a major cause of morbidity and mortality in patients with Cushing's syndrome. The pathogenesis of blood pressure elevation is multifactorial and not completely understood: it may include increased peripheral vascular sensitivity to adrenergic agonists, increased hepatic production of angiotensinogen and activation of MRs by cortisol. The diagnosis of Cushing's syndrome relies first on urinary or salivary cortisol measurement and low-dose dexamethasone suppression tests; when unregulated hypercortisolism is demonstrated, plasma ACTH measurement allows differentiation of ACTH-dependent (due to a pituitary or non-pituitary ACTH-secreting tumor) from the less frequent ACTH-independent (due to an adrenal source) forms.[18,19] Thereafter, imaging and venous sampling techniques allow more precise identification of the cause. In most cases, the treatment of Cushing's disease is aimed at finding and surgically (or radiotherapeutically) removing the cause of excess glucocorticoids, i.e. a pituitary or adrenal adenoma. This intervention usually results in correction, or at least improvement, of the hypertensive state; however, pharmacological antihypertensive treatment may be necessary for a prolonged period or even indefinitely in these patients.

## Pheochromocytoma

The term pheochromocytoma identifies a category of tumors originating from catecholamine-producing chromaffin cells located in the adrenal medulla and sympathetic paraganglia. Pheochromocytoma is a rare disease, with a reliable estimate of its incidence being approximately one case per 100,000 subject-years. The most frequent clinical presentation is hyperadrenergic syndrome, with persistent or paroxysmal hypertension (either true paroxysm or crises superimposed

on sustained hypertension) as a leading sign. The diagnosis of pheochromocytoma is relatively straightforward provided the suspicion is raised. Besides patients with a suggestive clinical picture, two conditions call for specific diagnostic investigation: subjects with incidentalomas and relatives of patients with a genetic predisposition to pheochromocytoma (see below). International guidelines do not recommend screening for pheochromocytoma in the general hypertensive population unless clinical data suggest the diagnosis.[11] The fundamental screening procedure is to obtain biochemical evidence of increased catecholamine production, possibly by measurement of plasma or 4-hour urinary fractionated metanephrines (see *Figure 2*).[20] In subjects with abnormally high values, imaging studies aimed at locate the tumor(s) are indicated (CT, magnetic resonance, $^{123}$I-labelled metaiodobenzylguanidine scanning). When the diagnosis of pheochromocytoma is made, surgical removal of the mass(es) should be performed, unless contraindicated. In any case, medical treatment with an adrenergic antagonist must be started immediately to block the deleterious effects of increased circulating catecholamines and to restore plasma volume (impaired by chronic vasoconstriction). The alpha-blocker phenoxybenzamine is still considered the drug of choice by many authors, but it is not available in many countries and can be effectively substituted by alpha-1 selective blockers (prazosin, doxazosin, and similar). Beta-blockers (preferably beta-1-selective) can be added to control tachycardia or arrhythmias, when present, but must be started after alpha-blockers to avoid hypertensive crisis due to loss of beta-2-mediated vasodilation. If adrenergic antagonists are insufficient to adequately control blood pressure, other antihypertensive agents (such as calcium antagonists) can be used. Surgical treatment has traditionally been performed through laparotomy, but the laparoscopic technique should now be considered the procedure of choice for most patients. Interestingly, many recent studies have consistently shown that a high percentage (approximately 15–30 %) of pheochromocytoma patients carry genetic mutations of pathogenic relevance, sometimes in the context of specific syndromes (MEN2, Von Hippel-Lindau disease, neurofibromatosis type 1).[21,22] Accordingly, we suggest performing a systematic screening for genetic predisposition should be performed in all patients diagnosed with pheochromocytoma, since the detection of a pathogenic mutation in apparently sporadic, non-syndromic pheochromocytoma patients may disclose the presence of the proband's relatives who also carry the mutation and are affected by subclinical disease.

### Thyroid Disease

Hypertension is present in many cases of hyper- or hypothyroidism.[23] In the presence of excessive amounts of circulating thyroid hormones there is increased sensitivity to circulating catecholamines, leading to a high cardiac output state and (mostly systolic) hypertension. The treatment of hyperthyroidism is obviously dependent on the specific cause; in general, beta-adrenergic blockers are the best choice to treat high blood pressure while waiting for normalization of thyroid hormone status, and have the additional advantage of controlling other signs of the hyperadrenergic state (tachycardia, tremors). In the presence of hypothyroidism, blood pressure rises as a consequence of increased peripheral vascular resistance. The severity of hypothyroidism seems to be correlated with diastolic blood pressure. Thyroid hormone replacement in hypertensive hypothyroid patients reduces both systolic and diastolic blood pressure, but in a few patients, particularly in the elderly and in presence of a long-standing hypertensive state, antihypertensive pharmacological treatment may also be necessary.

### Hyperparathyroidism

Blood pressure increase is frequently seen in association with primary hyperparathyroidism, even among those with mild disease.[24] The mechanisms underlying this association are poorly understood and the causal relationship has been questioned. Among other possibilities, a direct effect of parathyroid hormone *per se*, hypercalcemia or the involvement of the RAS and the sympathetic nervous system have been considered. There is also controversy about the effectiveness of parathyroidectomy to reverse hypertension. The prevalent opinion is that the presence of hypertension in patients with primary hyperparathyroidism is not an indication for surgical intervention.

### Acromegaly

Irrespective of the cause (mostly benign, growth-hormone-secreting pituitary adenomas), acromegalic patients of both sexes have an increased prevalence of hypertension compared with matched controls (approximately 1.5-fold higher).[25,26] Blood pressure elevation affects both systolic and diastolic values and appears to be related to the increased plasma volume and total exchangeable sodium pool, but hypertrophic remodelling of subcutaneous small resistance arteries[27] and glucose tolerance abnormalities[28] may also play a role. High blood pressure may interact with other growth-hormone-dependent signals in the development of acromegalic cardiomyopathy, characterized by left ventricular hypertrophy and interstitial fibrosis.[26] Successful treatment leading to adequate control of growth hormone levels is accompanied by a substantial improvement of both morphological and functional cardiovascular abnormalities and may also cure or at least ameliorate the hypertensive state, particularly in young patients and those with recent-onset disease.

## Conclusions

Arterial hypertension is a common feature in diabetes and several other endocrine syndromes. An increase in blood pressure can be produced by many different mechanisms and often substantially contributes to the morbidity and mortality of these diseases. As a consequence, early diagnosis and appropriate treatment may significantly affect the prognosis in these patients. ■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