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# A Textbook on Endocrine Hypertension: Your Key for Better Understanding

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## Introduction

Hypertension is one of the most common chronic non-communicable diseases affecting 30-40% of the adult population worldwide, and according to the 2021 estimate of the World Health Organisation (WHO), 1.28 billion adults aged between 18 and 79 years are affected globally. The majority (≈85%) of these patients suffer from primary or essential hypertension where there is no underlying cause. The remainder has secondary hypertension caused by one of the several known conditions which may be potentially curable by appropriate timely diagnosis and management. Secondary hypertension often presents as resistant hypertension - defined as blood pressure that remains above 140/90 mmHg despite the use of three antihypertensive medications of different classes at the maximally tolerated doses, one of which is a diuretic [1]. Approximately 10% of patients treated for hypertension have resistant hypertension [1]. The prevalence of secondary hypertension is around 30% in patients with resistant hypertension, whereas its prevalence is only 5-15% in non-selected hypertensive population [2]. Hence, it is important that patients with resistant hypertension undergo workup to identify a potential secondary cause [3]. The prevalence of secondary hypertension in patients with hypertension under the age of 40 years is close to 30% [4]. This high prevalence necessitates a systematic work-up for secondary hypertension in young adults, even outside the resistant hypertension range.

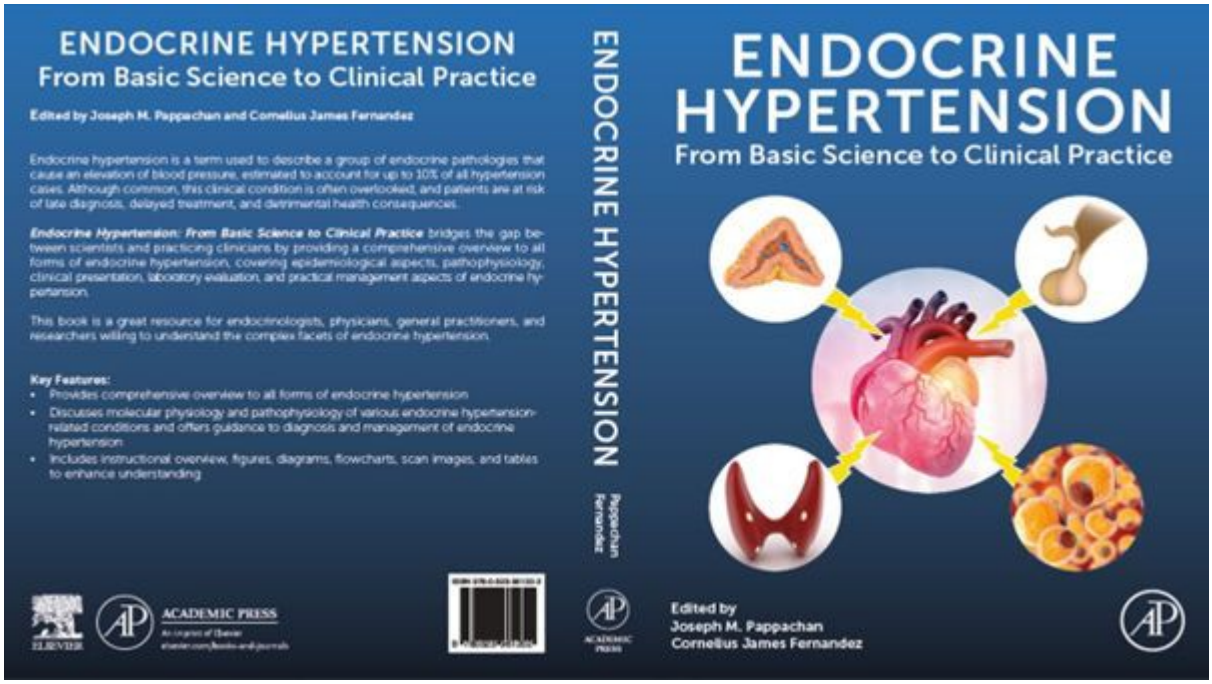
## Endocrinology and blood pressure

The endocrine causes of secondary hypertension (commonly known as endocrine hypertension) are increasingly being identified as our diagnostic armamentarium improved in the recent years. They are now among the most frequent causes of secondary hypertension, and with the recognition of the increased prevalence of primary aldosteronism, they could represent up to 20% of all patients with hypertension [5]. Searching for endocrine hypertension can be a highly rewarding experience for

both patients and physicians, as a clinician who identifies a treatable endocrine disease as the cause of his patient's hypertension can greatly improve the outcome by appropriate medical or surgical intervention. But this requires a high index of suspicion and a systematic approach. The textbook "***Endocrine Hypertension: From Basic Science to Clinical Practice***" edited by Joseph M. Pappachan and Cornelius J. Fernandez is an excellent resource providing the latest available evidence on this topic with a very systematic approach to these disorders.

**An overview**

The soft cover of the book has a beautiful self-explanatory image that gives a clear indication of what the book contents would be about. This first edition of the book has 381 pages, and it is published on 26th of October 2022. The publisher is ***Academic Press (Elsevier), and ISBN is 9780323961202***. Flipping through the pages, we are happy to note that the chapters are well organised with beautiful figures, tables and graphical abstracts that makes it easily readable and quite user-friendly. The design, layout, font type and font size seem very appropriate. The paper quality is excellent. This book is meant for endocrinologists, cardiologists, physicians, general practitioners, researchers, and medical trainees of all disciplines who are eager to understand the complex facets of endocrine hypertension. Though the chapter authors are from 12 different countries of the world across 5 continents, the book maintains a very professional language throughout. We feel that the authors succeeded in communicating the important learning points to every reader of the book. Few quotes from authors that we found useful can be found in the following paragraphs.




**Basic science**

It is essential to learn basic physiology for the better understanding of pathophysiology. The initial basic science chapters of this book (chapters 2 to 6) made the complex topic quite simple with the help of many beautiful figures, flow charts and algorithms [6-10]. The chapters on various aetiologies of endocrine hypertension including primary aldosteronism [11] (chapter 7), familial hyperaldosteronism [12] (chapter 8), congenital adrenal hyperplasia [13] (chapter 9), other inherited causes [14] (chapter 10), pheochromocytoma [15] (chapter 11), paraganglioma [16] (chapter 12), ACTH dependent Cushing's syndrome [17] (chapter 13), Adrenal Cushing's syndrome [19] (chapter 14), Acromegaly and Growth Hormone deficiency [20] (chapter 15), thyroid disease and primary hyperparathyroidism [21] (chapter 16), and obesity, insulin resistance and obstructive sleep apnoea [22] (chapter 17) discussed the pathophysiology, epidemiology, clinical features, diagnosis, and

management of individual diseases. Several authors of this textbook either discovered the culprit genes causing one or other forms of the endocrine hypertension or first described the clinical entity associated with the endocrinopathy. This also makes this textbook unique in its scientific authenticity.

Many causes of endocrine hypertension are monogenic - associated with single genetic alterations that follow a Mendelian inheritance (either gain-of-function or loss-of-function mutations). Hence, genetic testing is important, and the editors have touched on this important aspect on chapter 1 of this book [23]. Authors of chapter 6 on Monogenic hypertension [10] writes: "diagnostic evaluation involves clinical profiling coupled with measurement of plasma renin, aldosterone, and electrolyte levels, and the analysis of disease-associated genes, which are increasingly performed using panel sequencing". The senior author of this chapter (Ute I Scholl) discovered 4 culprit genes associated with familial hyperaldosteronism (FH).

**Clinical aspects**

Although primary aldosteronism (PA) is probably the most common form of endocrine hypertension, the clinical suspicion and diagnostic evaluation is often inadequate among medical practitioners. Chapter 7 "Primary aldosteronism (Conn's syndrome)" provides a clear, logical, and practical approach to the disease with an up-to-date evidence base [11].

Chapter 8 gives a vivid picture on familial hyperaldosteronism (FH) and summarises clinical, diagnostic, and therapeutic aspects of the rare disorders causing FH and portrays the molecular and genetic aspects of these uncommon conditions [12]. Various forms of FH are associated with early-onset monogenic hypertension with a strong family history and accounts for only a small proportion of patients with PA. The disease severity may vary depending on the degree of penetrance. While glucocorticoid-remediable aldosteronism (GRA) is the most common form of monogenic hypertension, the other varieties of FH are very rare. Diagnostic work up of FH involves biochemical confirmation of PA followed by appropriate molecular genetic analysis to identify the culprit gene causing the disease. Newer genes associated with both familial and sporadic PA are still being discovered improving our understanding of these genetic disorders. Early diagnosis of these disorders especially GRA is of paramount importance as delay is associated with catastrophic complications such as cardiovascular mortality.

The authors of chapter 9 on congenital adrenal hyperplasia [13] suggest that "clinicians should screen children, adolescents, and young adults who present with hypertension, hypokalemia, and low aldosterone and renin levels. In addition, hyperpigmentation, muscle weakness, delayed or precocious puberty, growth failure, ambiguous genitalia, and virilization are important clues to diagnosis. Authors propose that 11β-hydroxylase deficiency should be considered in females with hyperandrogenaemia signs such as hirsutism, clitoromegaly, menstrual irregularities, cystic acne, male pattern baldness, increased muscle mass, masculine body habitus, and in males with pseudo precocious puberty when presented to clinicians with young-onset hypertension. 17α-hydroxylase deficiency may be the reason for early onset hypertension in a female phenotype without secondary sexual characteristics, with hypergonadotropic hypogonadism".

The experts writing chapter 11 on pheochromocytoma [15] suggest that "solitary elevation of metanephrines or normetanephrines by 2-fold or simultaneous elevation of two or more metabolites (metanephrines, normetanephrines, and/or 3-methoxytyramine) are less likely to be false-positive. These situations necessitate further diagnostic imaging, regardless of the pre-test probability. On the other hand, in those with less than 2-fold elevation of a single metabolite with no other possible explanation for a false-positive test result, especially in those with a high pre-test probability for pheochromocytoma/paraganglioma (PCC/PGL) based on the clinical score, a clonidine suppression

test can be done to differentiate the false-positive test from the true-positive. However, those with a low pre-test probability for PCC/PGL do not need any further tests".

In chapter 12, on paraganglioma16, the authors write: "In contrast to pheochromocytoma (Cluster 2-related genes), in which mutations may occur at germline or somatic genes, most paragangliomas or PGLs-related mutations are reported only as germline, except for Cluster 1B-related PGLs, which are more frequently somatic. Underlying mutations predispose to specific tumor development, metastatic or multifocal involvement, disease penetration, and other syndrome-related tumors". Therefore, all subjects with PGLs should be involved in the discussion about genetic testing, irrespective of age or tumor location. This is performed using next-generation sequencing, either on DNA acquired from peripheral blood or buccal smear or, more recently, from resected tumor tissue. The latter approach enables not only the identification of germline mutations (mutation found in tumorous and peripheral DNA), but also somatic mutations (mutation found only in tumorous DNA).

The authors of chapter 13 ACTH dependent Cushing's syndrome [17] suggest that achievement of eucortisolism by successful surgery, generally results in significant improvement of hypertension, though often does not eradicate it. "While the patient is awaiting surgery, treatment of hypertension should be implemented to reduce the risk of cardiovascular events. Postoperatively, antihypertensive agents may need to be reduced, or even discontinued to prevent hypotension and hyperkalemia especially in patients who achieve biochemical remission. Patients with persistent CS treated medically may also require ongoing antihypertensive treatment". Two of the authors of this chapter are kingmakers of the latest guidelines on Cushing's disease too [18].

Based on the latest evidence, Ragnarson O, the author of chapter 14 "Adrenal Cushing's syndrome" proposes that preoperative therapy with adrenal steroidogenesis inhibitors is effective in lowering the cortisol concentrations, and subsequently in reducing the blood pressure and the plasma glucose concentrations [19]. "Cortisol-lowering medical therapy alone is not always sufficient in reducing the high blood pressure in patients with CS. In these cases, mineralocorticoid receptor antagonists are often useful, especially in patients with moderate to severe hypercortisolemia and/or hypokalemia. Based on studies on the pathophysiology of hypertension in patients with CS, ACE inhibitors or ARBs are also considered to be a good choice, either as monotherapy or in combination with CCBs. Perioperative thromboprophylaxis with low molecular weight heparin should be considered in all patients with CS, especially in patients with moderate to severe hypercortisolism. Prophylactic broad-spectrum antibiotics as well as prophylactic treatment against Pneumocystis jirovecii should be considered, especially in patients with severe hypercortisolism".

The authors of chapter 15 on Acromegaly and Growth Hormone deficiency [20] summarises that "secondary hypertension due to acromegaly should be suspected especially in those patients with acral enlargement and facial features. In patients without typical manifestations, the suspicion of acromegaly should be raised in hypertensive patients who have several of these associated conditions: sleep apnoea syndrome, diabetes mellitus (type 2), debilitating arthritis, carpal tunnel syndrome, and hyperhidrosis. Biochemical screening of every hypertensive patient systematically for acromegaly is not recommended. The clinical suspicion of an acquired growth hormone deficiency (AGHD) in patients with hypertension should be considered in patients with structural hypothalamic and/or pituitary disease, surgery/irradiation in these areas, head trauma, or evidence of other pituitary hormone deficiencies. The presence of a low IGF-1 increases the likelihood of GHD; however, around a fifth of AGHD patients, particularly males, may exhibit normal IGF-1 levels".

In chapter 16, which focuses on thyroid disease and primary hyperparathyroidism [21] the author states that "endocrine causes of hypertension, thyroid disorders are less prominent than pheochromocytoma, primary aldosteronism, and Cushing's syndrome. However, disorders of thyroid function are relatively common in the general population and very easily treatable. Therefore, clinical assessment for thyroid disease and use of TSH measurement for case finding in hypertensive

patients is an easy adjunct, and therefore recommended". They continue "Clearly, if symptoms suggestive of hypercalcemia are present, or if renal impairment, nephrocalcinosis, or a history of renal calculi accompany a diagnosis of hypertension, then primary hyperparathyroidism should be excluded. In a practical sense, all hypertensive patients should have hypercalcemia excluded during evaluation of their hypertension".

The global obesity pandemic has resulted in a significant increase in the prevalence of obstructive sleep apnoea which is often ignored as a major health problem by medical professionals because of poor awareness and vague symptomatology. The authors of chapter 17 state that the effects of obesity on the development of insulin resistance and primary hypertension become complicated in the context of obstructive sleep apnoea (OSA)22. "OSA itself is an independent risk factor for the development of insulin resistance. Therefore, in people with obesity who also develop OSA, a metabolic "double-whammy" exists in which obesity-related insulin resistance is intensified by the independent effects of OSA. In the case of hypertension, there are additional complexities that implicate recurrent nocturnal sympathetic overdrive and activation of the renin-angiotensin-aldosterone system (RAAS), each of which typifies OSA. Such effects further drive heightened blood pressure and contribute toward the development of OSA-related secondary hypertension (ORSH), which is often resistant to therapies".

**Diagnostic approach**

Imaging confirmation of the disease is the final step in the clinical diagnosis of any endocrinopathy including various disorders associated with endocrine hypertension. In the chapter 20, "Imaging for patients with endocrine hypertension" the authors summarise the best evidence with the aid of very classical images of different diseases associated endocrine hypertension [24]. The authors state that the role of imaging extends from detecting and characterizing hyperfunctioning endocrine lesions, assisting surgical planning, and staging malignancy where relevant. Close collaboration between endocrinologists, endocrine surgeons, and radiologists is essential to ensure best patient outcomes in the management of endocrine hypertension.

The authors of chapter 21 "Systematic approach to the diagnosis and management of endocrine hypertension" gives an excellent summary of the whole theme of this textbook. [25] They propose consideration of an underlying endocrine cause of hypertension in all hypertensive patients but especially those with early onset, resistant, accelerated/malignant hypertension, or with hypokalemia, symptoms/signs of known causative endocrine conditions, incidentally-discovered adrenal lesions or having a family history of hypertension or stroke. "Consider screening for PA in all newly diagnosed hypertensives. Although rare, pheochromocytoma is a potentially dangerous condition and the diagnosis should not be missed, arguing for a low threshold for screening among patients with hypertension even when typical symptoms are lacking. The demonstration of renal artery stenosis in a hypertensive patient does not necessarily establish it as the cause of hypertension: functional testing such as renal venous renin assessment can assist in selecting patients who are likely to benefit from intervention".

**Summary**

Overall, this textbook ***"Endocrine Hypertension: From Basic Science to Clinical Practice"*** edited by Joseph M. Pappachan and Cornelius J. Fernandez gives us a good learning experience. The book is of optimum length, giving sufficient clear knowledge for a practising physician. The authors maintained good continuity and clarity of thoughts. The readers shall surely find this textbook very useful and fulfilling their learning needs. The textbook can be recommended as a classical reference guide and practice manual for medical practitioners in clinical practice and basic scientists involved in research. It will be value for money for those who purchase the book.

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