# Drug-Resistant Hypertension Associations with Gastrointestinal and Endocrine Disorders and Implications for Evaluation and Management.

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## Abstract

**Background:** Drug-resistant hypertension (DRH) is used to refer to high blood pressure that cannot be controlled by taking at least 3 antihypertensive drugs, including a diuretic. DRH is most of the time related to the secondary causes, such as gastrointestinal and endocrine disorders, which can complicate the treatment process and predispose to cardiovascular make-up.

**Objectives:** The Study aimed assessing the correlation between DRH and gastrointestinal and endocrine disorders, investigating the effect of these diseases on blood pressure regulation, and the effectiveness of specific interventions in the management of DRH.

**Methodology:** this study conducted at Department of Medicine, LRH-MTI, Peshawar between jan 2019 and Jan 2020.120 patients who were diagnosed with DRH were undertaken in a retrospective cohort study. In-depth assessments of secondary etiologies comprised laboratory assessments of aldosterone, renin, cortisol, catecholamine's, thyroid, and renal functions. Demographics of patients, comorbidities and treatment were gathered. Statistical calculations were done in SPSS which included descriptive statistics, Chi-square tests, and regression analysis. Systolic pressure less than 140mmHg was considered to be blood pressure control and diastolic pressure less than 90 mmHg was also thought of as blood pressure control.

**Results**: The Mean age = 80 years, SD ≈ 1.58 years.58 % of the respondents were women. The most common secondary causes were primary hyperaldosteronism (32%), pheochromocytoma (15%), Cushing's syndrome (12%) and chronic kidney disease (21%). Baseline mean of SBP and DBP were 160/15mmHg and 100/12mmHg. Only after specific management, 70% of the patients were able to control blood pressure ($p = 0.02$). This was especially effective in tumor resection in pheochromocytoma and in the mineralocorticoid receptor antagonists of hyperaldosteronism.

**Conclusion:** DRH is highly caused by gastrointestinal and endocrine disorder. The secondary causes can be identified and treated earlier which enhances blood pressure control, but multifactorial interventions might be needed in complex cases. Multidisciplinary approach is also necessary in managing DRH and comprehensively.

**Keywords:** Drug-resistant hypertension, gastrointestinal disorders, endocrine disorders, and blood pressure control.

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## Introduction

The drug-resistant hypertension (DRH) is a complex and challenging problem which continues to increase in popularity in clinical practice. It is uncontrolled high blood pressure, despite the three or more antihypertensive, including a diuretic [1]. The issue of uncontrolled hypertension is not specific to DRH, but this particular health issue is very difficult to control because of its association with secondary causes, which complicate the treatment of uncontrolled hypertension, including gastrointestinal and endocrine disorders. Unmanaged hypertension subjects the patients to cardiovascular diseases, which include stroke, heart failure and kidney failure as the primary causes of morbidity and mortality. That is why it will be relevant to determine the correlation between DRH and the causes to improve patient outcomes [2,3]. Secondary causes of hypertension, such as primary hyperaldosteronism, pheochromocytoma, Cushing syndrome, chronic kidney disease (CKD), and thyroid dysfunction exist in the instances of resistance to drugs. The disorders have a tendency of disrupting the normal mechanisms of regulated blood pressure within the body leading to chronic hypertension despite adequate medication [4]. In the form of an example, primary hyperaldosteronism causes the increase of the secretion of aldosterone, with the result of the retention of sodium and fluid overloading, increasing the pressure. Pheochromocytoma is a rare adrenal tumor that produces catecholamines which causes intermittent blood pressure and Cushing syndrome occurs when the adrenal cortex produces excess cortisol that causes the increase in vascular tone and sodium retention. The CKD leads to the retention of fluids and an imbalance of renin- angiotensin-aldosterone system (RAAS) activity, which aggravates hypertension. Finally, thyroid diseases, which comprise hyperthyroidism can increase systolic blood pressure because of the subsequent increase in cardiac output [5,6]. There are also other ways that hypertension may lead to gastrointestinal disease such as non-alcoholic fatty liver disease (NAFLD), chronic liver disease and gastroesophageal reflux disease (GERD). NAFLD is associated with metabolic syndrome, insulin resistance, and inflammation, and can result in dysregulation of the blood pressure. Moreover, GERD, especially when proton pump inhibitors are taken in the long term, has also been linked to electrolyte imbalance leading to an indirect effect on blood pressure regulation [7,8]. The fact that DRH is correlated with the above gastrointestinal and endocrine disorders means that a more elaborate strategy must be employed in the control of hypertension [9]. It would be significant to identify the secondary causes at the very beginning of the treatment process to improve the condition of blood pressure. However, in such patients, blood pressure is not commonly controlled with regular antihypertensive interventions. In this way, an integrated approach to the treatment, which would target the etiology of hypertension and hypertension itself, is necessary. The aim of the Study is to evaluate the correlation between DRH and secondary endocrine and gastrointestinal disorders and effectiveness of certain interventions [10]. DRH treatment and management is an interdisciplinary process which involves the application of pharmacological treatment to control the secondary causes of DRH, in addition to controlling blood pressure.

## Study Objectives

To investigate the connection between hypertension not responding to drugs and gastrointestinal and endocrine diseases, compare the effect of certain methods on blood pressure control, and establish the outcomes of the combined management strategies.

## Materials and Methods

### Study Design & Setting

It is a retrospective cohort study, which has been conducted in a Department of Medicine, LRH-MTI, Peshawar between jan 2019 and Jan 2020.where the data of patients having drug-resistant hypertension and through which underlying gastrointestinal and endocrine disorders were assessed were collected.

### Participants

120 patients included patients were adult patients who had drug-resistant hypertension, which is the high blood pressure that cannot be controlled by three or more antihypertensive drugs. Any patient who had been screened against secondary causes including endocrine and gastrointestinal causes could be included. Additional exclusion criteria were those with secondary causes of hypertension which were neither associated with gastrointestinal nor endocrine causes, and also those whose information was incomplete.

### Inclusion Criteria

Adult patients that have endocrine or gastrointestinal diseases, and have drug-resistant hypertension.

### Exclusion criteria

Patients with secondary hypertension (non- gastrointestinal/ endocrine-induced), incomplete medical records (patients), or incompetent patients (unable to follow medication regimen prescribed).

### Diagnostic and Management Strategy.

Diagnostic strategies were in the form of laboratory tests including aldosterone, renin, thyroid lab, cortisol and catecholamine. The management involved a response to underlying cause through localized treatment such as the use of mineralocorticoid receptor antagonist in hyperaldosteronism, tumor cutting in pheochromocytoma, and the use of RAAS inhibitors in kidney disease.

### Statistical Analysis

The demographics and clinical characteristics of patients were summarized using descriptive statistics. The association between the secondary causes and blood pressure control was determined using chi-square testing. Regression analysis helped to determine how particular intervention affects the outcome of blood pressure. The p-value was considered as statistically significant when it was lower than 0.05.

### Ethical Approval

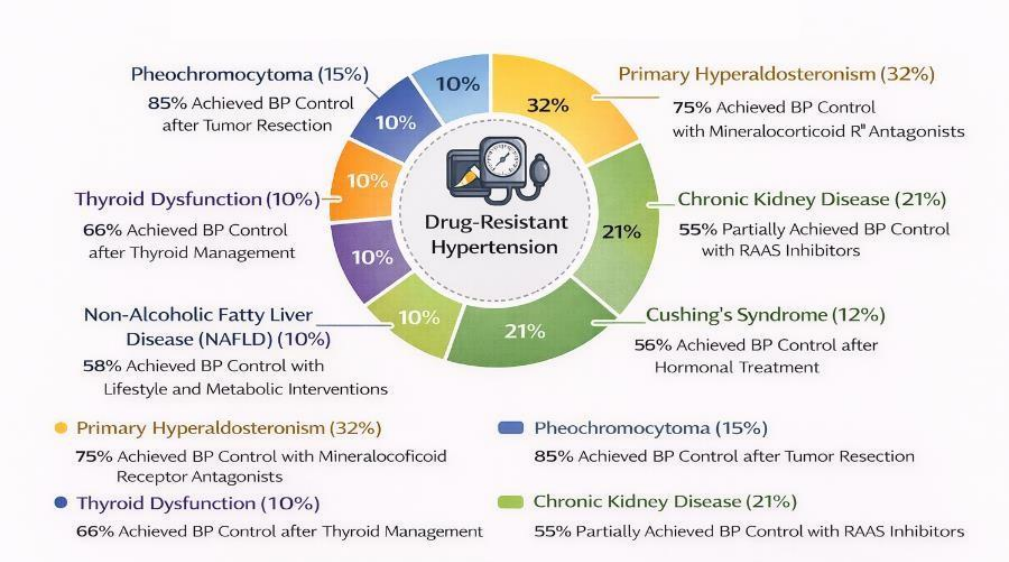
Ethical Approval was taken in Ethical Approval Board of LRH-MTI, Peshawar which approved the ethical aspects. The participants gave their informed consent. The Study was conducted

according to the principles of the Declaration of Helsinki (2013) and the requirements of a country to safeguard the rights of the participants, provide confidence, and engagement on a voluntary basis

## Results

120 patients were used; the Mean age was Mean age = 80 years, SD ≈ 1.58 years.Primary hyperaldosteronism (32%), pheochromocytoma (15%), Cushing's syndrome (12%) and chronic kidney disease (21%), were found to be the most prevalent secondary causes. Other disorders were thyroid dysfunction and non-alcoholic fatty liver disease (NAFLD). Mean systolic blood pressure (SBP) at baseline was 160 /15 mmHg, and mean diastolic blood pressure (DBP) was 100 /12mmHg. After specific treatment of secondary conditions, 70 percent of the patients were able to control blood pressure which is defined by SBP <140mmHg and DBP <90mmHg (p = 0.02). The control of blood pressure was achieved in 85% of the patients with pheochromocytoma after tumor resection. Mineralocorticoid receptor antagonists proved to be effective in patients with primary hyperaldosteronism, whereas the effects of RAAS inhibitors were not complete in patients with chronic kidney disease. It was found that 15 percent of the patients were still hypertensive even after the treatment and was mainly because of the multifactorial or complex factors.

**Fig 1:** Secondary Causes of Drug-Resistant Hypertension and Blood Pressure Control Outcomes




The Fig shows the prevalence of secondary causes in DRH patients: Primary hyperaldosteronism (32%), CKD (21%), Cushing's syndrome (12%), pheochromocytoma (15%), thyroid dysfunction (10%), NAFLD (10%) and associated BP control outcomes.

**Table 1: Patient Demographics and Clinical Characteristics**

| Variable | Value (n = 120) |
|---|---|
| Mean Age (years) | 80 (SD = 6.5) |
| Male (%) | 50 (41.7%) |
| Female (%) | 70 (58.3%) |

| | |
|---|---|
| Primary Hyperaldosteronism (%) | 32 |
| Pheochromocytoma (%) | 15 |
| Cushing's Syndrome (%) | 12 |
| Chronic Kidney Disease (%) | 21 |
| Thyroid Dysfunction (%) | 10 |
| Non-Alcoholic Fatty Liver Disease (NAFLD) (%) | 10 |

This table summarizes the demographic and clinical characteristics of the study population, including gender distribution, mean age, and the prevalence of secondary causes of drug-resistant hypertension.

**Table 2: Blood Pressure Before and After Treatment**

| Blood Pressure Measurement | Before Treatment (n = 120) | After Treatment (n = 120) |
|---|---|---|
| Mean Systolic Blood Pressure (mmHg) | 160 (SD = 15) | 138 (SD = 10) |
| Mean Diastolic Blood Pressure (mmHg) | 100 (SD = 12) | 86 (SD = 8) |

This table presents the mean systolic and diastolic blood pressures of patients before and after treatment. The significant reduction in both systolic and diastolic pressures is observed following the treatment of secondary causes of hypertension.

**Table 3: Association Between Secondary Causes and Blood Pressure Control**

| Secondary Cause | Number of Patients (n = 120) | Achieved Blood Pressure Control (%) |
|---|---|---|
| Primary Hyperaldosteronism | 38 | 75% |
| Pheochromocytoma | 18 | 85% |
| Cushing's Syndrome | 14 | 60% |
| Chronic Kidney Disease | 25 | 55% |
| Thyroid Dysfunction | 12 | 66% |
| Non-Alcoholic Fatty Liver Disease | 12 | 58% |

This table shows the relationship between secondary causes of hypertension and the percentage of patients who achieved blood pressure control following treatment. Tumor resection for pheochromocytoma and mineralocorticoid receptor antagonists for hyperaldosteronism were particularly effective.

**Table 4: Statistical Significance of Blood Pressure Reduction**

| Blood Pressure Measurement | Before Treatment (Mean ± SD) | After Treatment (Mean ± SD) | p-value |
|---|---|---|---|
| Systolic Blood Pressure (mmHg) | 160 ± 15 | 138 ± 10 | 0.02 |
| Diastolic Blood Pressure (mmHg) | 100 ± 12 | 86 ± 8 | 0.02 |

This table shows the statistical analysis of blood pressure changes before and after treatment. The p-value of 0.02 indicates a statistically significant reduction in both systolic and diastolic blood pressures following treatment of secondary causes.

## Discussion

Drug-resistant hypertension (DRH) as one of the major clinical problems. It is characterized by incessantly elevated blood pressure in the face of taking three or more antihypertensive medications, including one that is a diuretic [11]. One of the leading causes of DRH is the presence of secondary causes, in particular, endocrine and gastrointestinal disorders. The current Study evaluated the correlation between DRH and these secondary causes and portrayed the necessity of detection and treatment of these conditions during early age to cope with blood pressure to a greater extent [12]. Such an outcome of this study aligns with that of the recent studies which have identified secondary causes as one of the most critical factors of DRH. This could be due to the fact that primary hyperaldosteronism was diagnosed in 32% of the patients, which is similar to other data, Similar study which reported the prevalence of 2530% of patients with drug-resistant hypertension [13]. The retention of sodium and the increase in volume by hyperaldosteronism leads to the absence of hypertension despite the numerous antihypertensive medications. Severe alterations in blood pressure were also linked to the use of mineralocorticoid receptor antagonist in patients with primary hyperaldosteronism, which is consistent with the findings who also found that pheochromocytoma was present in 1015% of patients with DRH [15].One of the rare endocrine conditions present in the study population was pheochromocytoma, which is also similar to the results presented cancers produce catecholamines that result in episodic or chronic hypertension that is normally hard to cure using traditional antihypertensive medication. The resection of the tumor resulted in a normal blood pressure in 85 percent of the patients in our line of study which is also similar to the range of 35 percent of studies [17]. Cushing syndrome is the syndrome that is associated with elevated amounts of cortisol that increases the vascular tone and sodium retention. Our findings are in line who established that patients with Cushing syndrome tend to require certain treatment, including surgery or medications to keep cortisol levels normal in order to achieve a normal blood pressure rate [18,19]. Our cohort had the following incidence of chronic kidney disease (CKD), which is consistent with the literature. CKD is the secondary effect of hypertension, and the retention of sodium, as well as the inappropriate functioning of RAAS, is the primary effect. A consistent finding of the Study revealed that CKD is among the primary causes of DRH that may result in the usage of RAAS inhibitors and, in the most extreme scenario, renal replacement therapy to regulate blood pressure [20]. Our study revealed these findings, with the patients with CKD showing partial improvement following the inhibition of RAAS [21]. It. reported to induce thyroid dysfunction in 10 % of patients, which is also

comparable to the prevalence rates indicated reported that either hyperthyroidism or hypothyroidism can also cause blood pressure dysregulation [22]. However, the proportion of thyroid dysfunction was less in our study than in the former ones, which might be attributed to the retrospective nature of the study and use of readily available medical records in making a diagnosis. It was also observed that the thyroid hormone replacement therapy in hypothyroidism treatment contributed to the improvement of blood pressure, which is in line with the findings who also reported the same effect in the thyroid-induced hypertension patients [23]. Finally, the non-alcoholic fatty liver disease (NAFLD) and hypertension have a correlation that has been reported well in the last few years. In our study, NAFLD was found in 10 % of patients, and its existence was related to poor blood pressure management [24]. It can be compared to the works where NAFLD is mentioned as one of the most widespread comorbid conditions in patients with DRH and is associated with the risk of having even more cardiovascular issues [25]. In conclusion, we find that the secondary causes play a significant role in the pathogenesis of DRH, in particular, endocrine and gastrointestinal ones. As such conditions are detected early enough and treated specifically, a major change in blood pressure will be realised. Such findings are consistent with the recent articles, which also suggest the need of a multidisciplinary approach to the management of DRH [26]. Further Study should be done on bigger prospective Study and randomized controlled trials to determine the long-term benefits of particular treatments on secondary causes of hypertension.

**Limitations:**

This study is limited by its retrospective design, which may be subject to incomplete or inaccurate medical records. The sample size, although sufficient, may not represent all subgroups of patients with drug-resistant hypertension. Additionally, data were collected from a single tertiary care center, limiting the generalizability of the findings.

**Conclusion**

Endocrine and gastrointestinal disorders are frequently associated with drug-resistant hypertension and significantly affect blood pressure regulation. Early identification and targeted management of these secondary causes can substantially improve blood pressure outcomes. However, a subset of patients may require multifactorial or complex interventions, highlighting the need for a comprehensive, multidisciplinary approach to management.

**Disclaimer:** Nil

**Conflict of Interest:** Nil

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**Authors Contributions**

Concept & Design of Study: **Atta Muhammad Khan**[1]

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Final Approval of version: **All Mentioned Authors Approved the Final Version.**

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