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Inflation of diagnostic tests in hypertensive young adults: a need for diagnostic guideline?

Research Article

Alper Kirkpantur, Mustafa Arici, Bulent Altun, Cetin Turgan

Hacettepe University Faculty of Medicine, Department of Internal Medicine, Nephrology Unit, 06500 Ankara, Turkey

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Abstract: The cause of hypertension in young adults (age:18-29 years) is mostly a primary condition although secondary causes are frequent in this population. Clinical files of 100 patients were reviewed to evaluate the use of diagnostic tests after completion of diagnostic work-up for hypertension. Seventy-nine patients had primary hypertention while 21 patients had secondary hypertension. Renal imaging studies, serum levels of aldosterone and plasma renin activity, and screening tests for pheochromocytoma were more likely to be performed in patients younger than 24 years, in female patients and in patients without familial history of hypertension in primary hypertensive patients ($p<0.05$). Renal imaging studies and screening tests for pheochromocytoma were done more frequently in patients with Stage 2 hypertension ($p<0,05$). Among secondary hypertensives, renal imaging studies and renal biopsy were more ordered in patients younger than 24 years, in female patients, in patients with Stage 2 hypertension and in patients without family history for hypertension ($p<0.05$). Mean body mass index was higher in patients with primary hypertension than patients with secondary hypertension ($p<0.05$). Seventy patients (70%) had undergone several screening interventions with negative results. In conclusion, a simple, stepwise diagnostic evaluation would greatly benefit the management of young hypertensives.

Keywords: *Hypertension • Secondary causes • Screening • Body mass index • Young adults*

1. Introduction

Cardiovascular diseases in adults usually find their roots in risk factors which operate in early stages of life and young adulthood [1]. Hypertension is associated with a worse cardiovascular prognosis independent of age [2]. As a result of increasing knowledge of the risks of hypertension, management of hypertension has become one of the most important indications for office visits to physicians in young people like the elderly. According to data from the National Health and Nutrition Examination Survey III, the prevalance of hypertension in the young adult population (aged 18-29 years) is 4 to 5% [3]. In Turkey, which is a developing country with a predominance of young adults (approximately one third of the adult population is between 18 and 30 years), the prevalance of hypertension in young adults (18-29 years) is 11.8% [4].

Young hypertensive patients usually presents a diagnostic dilemma and are frequently screened for secondary causes often seen in this age group. Renovascular hypertension, for example, is one of the more common forms of secondary hypertension, and medial fibromuscular dysplasia is usually noted in young women [5]. Despite the increased frequency of secondary hypertension in this population, there is no well defined screening method for secondary causes. The aim of this study was to evaluate the rational use of the diagnostic tests performed for young hypertensive patients admitted to a hypertension clinic of a tertiary medical center.

2. Material and Methods

A retrospective examination of office records was performed to identify the use of diagnostic tests in young adults who were referred for evaluation of hypertension between December 2002 and January 2004, to the Hypertension and Renal Unit at Hacettepe University Hospital in Ankara, Turkey.

* *E-mail: alperkirkpantur@yahoo.com*

Male and female young adults (aged 18-29 years) who had elevated blood pressure, were selected for participation in the present research. Patients were excluded from the sample if they were younger than 18 years or older than 29 years. Five specialists in clinical nephrology and hypertension participated in this study. For each physician, all relevant medical records were identified and reviewed in alphabetic order until 20 hypertensive young adult patients were identified.

The clinical files of patients were reviewed after the diagnostic work-up for hypertension had been completed. Data included demographic characteristics, etiology of hypertension (primary or secondary), stage of hypertension according to the report of the Seventh Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) [6], presence of familial history of hypertension, and body mass index (BMI) (kg/m^2) were collected. The BMI data was categorized according to numerous clinical consensus panels and public health organizations which define persons with a BMI of 30 or higher as obese, and a BMI value between 25 and 29.9 as overweight [7].

Information about routine laboratory tests for hypertensive patients (12-lead electrocardiogram, urinalysis, blood glucose and hematocrit, serum potassium, creatinine, calcium, a lipid profile that includes total serum cholesterol, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol and triglycerides) were also noted. Diagnostic tests to identify a secondary cause, such as Doppler ultrasonography of renal arteries (Doppler USG), captopril enhanced renal scintigraphy, magnetic resonance angiography for renal arteries (MR Angio), selective renal angiogram, renal ultrasonography (Renal USG), serum levels of aldosterone (Ald) and plasma renin activity (PRA), 24-hour urinary metanephrine and normetanephrine values as a screening test for pheochromocytoma were also recorded.

The Ethics Committee of Hacettepe University Hospital in Ankara, Turkey approved the study according to the standards of the Helsinki Declaration.

2.1. Statistical Analysis

The overall prevalance of primary and secondary hypertension, the demographic data, the distributions of the diagnostic tests in the study population were analyzed using SPSS version 10.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Descriptive data was presented as mean±SD. Student's t-test was used to compare values that were normally distributed and where appropriate the chi-square test was used to compare variables. P-values of less than 0.05 were considered to be statistically significant.

3. Results

3.1.Patient Characteristics

The clinical records of 100 hypertensive young adults (50 females and 50 males, mean age: 24.5±4.8 years) were retrospectively reviewed in this study. The mean±SD systolic and diastolic blood pressure values were 157.2±7.8 mm Hg (range, 140 to 170 mm Hg) and 94.7±4.4 mm Hg (range, 85 to 100 mm Hg), respectively. Classification of blood pressure values according to JNC-VII indicated that 66 patients (66%) had Stage 1 and 34 patients (34%) had Stage 2 hypertension. Family history for hypertension was recorded in 65 patients (65%).

3.2. Results of First Set of Tests

All of the patients had undergone medical evaluation consisting of a 12-lead electrocardiogram (ECG), urinalysis, blood glucose and hematocrit, serum potassium, creatinine, calcium and a lipoprotein profile that includes total serum cholesterol, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol and triglycerides.

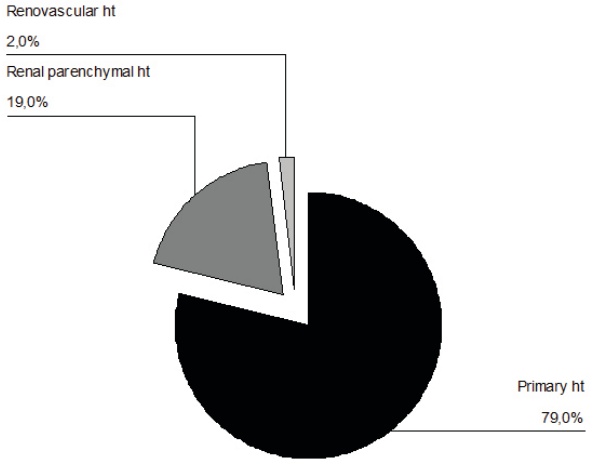
Blood chemistry studies did not reveal any abnormal value in calcium, glucose, potassium concentrations and blood hematocrit levels. However, serum creatinine level was found to be elevated in 19 patients and urinalysis was indicative of renal parenchymal disease in these patients, presenting with microscopic hematuria, erythrocyte and leukocyte casts. A renal biopsy was performed in these patients later on and were all subsequently diagnosed with acute glomerulonephritis. Studies on lipoprotein profile demonstrated dyslipidemia in a considerable amount of the patients-total 35 of 100 cases and all of the cases with renal biopsy. ECG studies did not provide additional information in subjects.

A total of 91 patients (91%) underwent further screening interventions due to strong evidence of renal disease (n=19), absence of family history of hypertension (n=32), patients with Stage 2 hypertension (n=20) and unknown or undetermined reasons-not stated in patient's clinical file (n=20).

3.3. Secondary Set of Diagnostic Tests

Additional diagnostic tests like Doppler ultrasonography (n=43), captopril enhanced renal scintigraphy (n=18), magnetic resonance angiography for renal arteries (n=4), selective renal angiogram (n=23), serum aldosterone and plasma renin activity (n=4), 24-hours urinary metanephrine and normetanephrine as screening test for pheochromocytoma (n=5), and renal ultrasonography (n=31), were performed in 91 patients to identify a secondary cause of hypertension.

Figure 1. Final diagnosis of etiology of hypertension and percentages in the study population (ht: hypertension).



One patient with a history of acute renal failure precipitated by therapy with an angiotensin converting enzyme inhibitor had positive findings for significant renal artery stenosis on Doppler ultrasonography. The final diagnosis was fibromuscular dysplasia (bilateral disease) by conventional angiography. Doppler ultrasonographic studies did not provide additional information on the remaining 42 patients. Isotopic renal scan was done in 18 patients. Among these patients, only one patient with an abdominal bruit on physical examination, had a positive captopril scintigraphy based on standard criteria. Selective renal angiogram was consistent with unilateral fibromuscular dysplasia in this patient.

On the revision of clinical files, 4 magnetic resonance angiography scans for renal arteries were performed. These scans were ordered in 4 female patients with a negative familial history of hypertension. Of 4 scans, none led to a diagnosis of renal artery disease as a cause of hypertension. Selective renal angiogram showed bilateral (1 patient) and unilateral (1 patient) fibromuscular dysplasia. The visualization of renal arteries was not helpful in medical work-up of remaining 21 patients.

Conventional renal ultrasonography was ordered in 31 patients. Of them, 19 patients had elevated serum creatinine levels and active urinary sediments. These patients had also undergone renal biopsy procedure. The reason for further evaluation by ultrasonography was to rule out autosomal dominant polycystic kidney disease in 12 patients. The determinations of serum aldosterone and plasma renin activity (n=4), urinary metanephrines and normetanephrines (n=5) did not support the clinical suspicion of adrenal disease.

Overall, 79 patients were diagnosed to have primary while 21 patients had secondary hypertension (Figure 1). Seventy patients (70%) had undergone

Table 1. Distribution of diagnostic tests according to clinical variables (age, gender, stage of hypertension according to JNC-7* and presence of family history of hypertension) among patients with primary hypertension.

Variable	Renal Doppler Usg*	Isotopic Renal Scan	Renal Mr Angio*	Selective Renal Angio*	Renal Usg*	Aldosterone and Pra*	Screening Test for Pheo*
Age (years):							
18-24	14/36**	6/36	3/36	11/36	6/36	3/36	4/36
24-29	20/43	8/43	1/43	11/43	6/43	1/43	1/43
	P=0.53	P=0.453	P=0.031	P=0.729	P=0.687	P=0.029	P=0.002
Gender:							
Female	22/39	12/39	3/39	14/39	8/39	3/39	5/39
Male	12/40	2/40	1/40	7/40	4/40	1/40	0/40
	P=0.025	P<0.001	P=0.041	P=0.001	P=0.015	P=0.001	P<0.001
Stage:†							
1	14/39	4/39	1/39	4/39	4/39	2/39	1/39
2	20/40	10/40	3/40	16/40	8/40	2/40	4/40
	P=0.04	P=0.002	P=0.046	P<0.001	P=0.015	P=0.262	P=0.006
Family History of Ht*:							
Present	11/56	2/56	0/56	3/56	8/56	0/56	1/56
Absent	28/23	12/23	4/23	18/23	4/23	4/23	4/23
	P<0.001	P=0.021	P=0.001	P<0.001	P=0.499	P=0.004	P=0.002

** JNC-7, the report of the Seventh Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; Usg, ultrasonography; Mr Angio, magnetic resonance angiography; Angio, catheter angiography; Pra, plasma renin activity; Pheo, pheochromocytoma; Ht, hypertension.*

*** a/b; a, number of patients in whom a certain test was performed; b, total number of patients.*

† Stage of hypertension according to JNC-7 report.

Table 2. Distribution of diagnostic tests according to clinical variables (age, gender, stage of hypertension according to JNC-7* and presence of family history of hypertension) among patients with secondary hypertension.

Variable	Renal Doppler Usg*	Isotopic Renal Scan	Renal Mr Angio*	Selective Renal Angio*	Renal Usg* and Renal Biopsy	Aldosterone and Pra*	Screening Test for Pheo*
Age(years):							
18-24	4/10**	2/10	0/10	2/10	10/10	0/10	0/10
24-29	5/11	2/11	0/11	0/11	9/11	0/11	0/11
	P=0.651	P=0.842		P<0.001	P=0.04		
Gender:							
Female	5/11	2/11	0/11	2/11	11/11	0/11	0/11
Male	4/10	2/10	0/10	0/10	8/10	0/10	0/10
	P=0.275	P=0.842		P=0.002	P=0.002		
Stage:†							
1	1/13	3/13	0/13	0/13	11/13	0/13	0/13
2	8/8	1/8	0/8	2/8	8/8	0/8	0/8
	P<0.001	P=0.32		P<0.001	P=0.001		
Family History of HT*							
Present	5/9	0/9	0/9	0/9	7/9	0/9	0/9
Absent	4/12	4/12	0/12	2/12	12/12	0/12	0/12
	P=0,402	P<0.001		P=0.005	P=0.005		

** JNC-7, the report of the Seventh Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; Usg, ultrasonography; Mr Angio, magnetic resonance angiography; Angio, catheter angiography; Pra, plasma renin activity; Pheo, pheochromocytoma; Ht, hypertension.*
*** a/b; a, number of patients in whom a certain test was performed; b, total number of patients.*
† Stage of hypertension according to JNC-7 report.

several screening interventions with negative results. There were no major differences in the results when comparing the five doctors.

3.4. Young Adults with Primary Hypertension

Among patients with primary hypertension (Table 1); MR Angio, Ald and PRA, and urinary metanephrine and normetanephrine levels were more likely to be performed in patients aged between 18-24 years than older patients (p<0.05). Female patients had more Doppler USG, captopril enhanced renal scintigraphy, selective renal angiogram, MR Angio, urinary metanephrine and normetanephrine levels, Ald and PRA and renal USG (p<0.05). Patients with negative family history for hypertension were more likely to have Doppler USG, captopril enhanced renal scintigraphy, MR Angio, selective renal angiogram, urinary metanephrine and normetanephrine levels and Ald and PRA (p<0.05). Finally, patients with Stage 2 primary hypertension had significantly more Doppler USG, captopril enhanced renal scintigraphy, selective renal angiogram, MR Angio, urinary metanephrine and normetanephrine levels and renal USG (p<0.05).

3.5. Young Adults with Secondary Hypertension

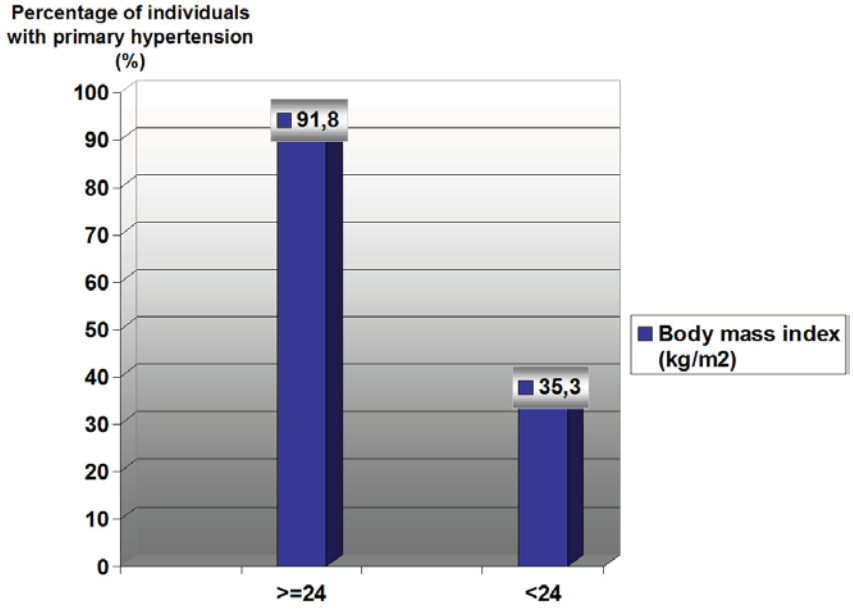
Table 2 shows the comparison of diagnostic tests in young adults with secondary hypertension according to age, gender, presence of family history and stage of hypertension according to JNC VII. There was a significant difference in ordering selective renal angiogram, renal USG and renal biopsy between patients with secondary hypertension aged 18-24 years and 24-29 years. Compared with male patients, female patients with secondary hypertension had more selective renal angiogram, renal USG and renal biopsy (p<0.05). Captopril enhanced renal scintigraphy, selective renal angiogram, renal USG and renal biopsy were performed significantly more frequent in secondary hypertensive patients with negative family history for hypertension. According to JNC VII, Patients with Stage 2 hypertension were more likely than patients with Stage 1 hypertension to have Doppler USG, selective renal angiogram, renal USG and renal biopsy . Finally, selective renal angiogram and urinary metanephrine and normetanephrine levels were significantly ordered more in secondary hypertensive patients than the primary hypertensive patients (Table 3).

Table 3. Distribution of diagnostic tests performed in patients with primary and secondary hypertension.

Tests	Patients withprimary hypertension (n=79)	Patients withsecondary hypertension (n=21)	P Value
Doppler ultrasonography of renal arteries	34	9	0.976
Isotopic Renal Scan	14	4	0.784
Magnetic resonance angiography of renal arteries	4	0	
Selective Renal Angiogram	21	2	<0.001
Renal Ultrasonography	12	19	0.167
Serum Aldosterone Level and Pra*	4	0	
Screening Tests for Pheochromocytoma	5	0	

**Pra, Plasma Renin Activity.*

Figure 2. Distribution of young adults with primary hypertension according to body mass index ($p<0.05$).



3.6. Body Mass Index and Etiology of Hypertension

The overall mean BMI was 23.9±5.3 kg/m^2 in the current study. According to international standards, 8 young adults (8%) were obese and 32 (32%) were overweight in the present work Comparison of BMI showed that young adults with primary hypertension had significantly higher BMI compared with those with secondary hypertension (25.2±2.3 vs 21.7±2.6 kg/m^2, $p<0.05$). The patients were categorized into 2 groups according to the median BMI value (24 kg/m^2). Average systolic (164±7 vs 145±9 mm Hg, $p<0.05$) and diastolic blood pressures (97±4vs 85±6 mm Hg, $p<0.05$), and prevalance of primary hypertension (Figure 2) were higher in patients with BMI ≥24 kg/m^2 than those with BMI<24 kg/m^2.

4. Discussion

The present study focuses on the use of diagnostic tests for hypertensive young adults (age range; 18 to 29 years) in a hypertension clinic of a tertiary medical center. It has been demonstrated that a more aggressive evaluation for secondary causes of hypertension would not significantly benefit these patients unless the presence of several strong clinical clues suggests secondary hypertension.

Although this study is a retrospective analysis, it represents a consecutive series of all young adult patients with newly diagnosed hypertension seen by a group of clinicians in our institution. After identification of the patients, clinical records were reviewed in alphabetic order for convenience. We planned and achieved to include 20 patients seen by any one physician. The

clinicians were chosen randomly. To the best of our knowledge, this study represents a significant study on pattern-of-practice analysis in young adults with newly diagnosed hypertension and we believe that the results of the study might reflect the practice patterns in this area.

The results showed a 21% prevalance of secondary hypertension in a population of hypertensive young adults. This proportion is higher than the widely known 5 to 10% prevalance of secondary causes in the general population [8]. This is not surprising as a certain cause may be responsible for up to 20% of all cases reported by investigators who are particularly interested in a particular category of hypertension and therefore see only a highly selected population [9]. Furthermore, it is widely known that the number of patients with hypertension of renal origin might vary with the setting. Severe hypertensive adolescents and young adults that are sent to a tertiary referral center for evaluation and treatment are most likely to have a renal basis of hypertension, whereas those with mild hypertension examined in primary care settings are more likely to have primary hypertension [10]. The clinic in which the study was carried out was a specialty referral clinic, receiving patients from primary care physicians for difficult to manage patients.

Overall, seventy patients (70%) had undergone several screening interventions with negative results. Physicians often face the difficult decision of which patients with hypertension to investigate for secondary causes. Several factors might play a role in influencing the diagnostic ordering of clinicians. An explanation for the high degree of screening in this study might be that the physicians do not want to miss a relatively frequent identifiable that presents in this age group. Perception of an identifiable cause of hypertension could be affected by the higher prevalence of fibromuscular disease in young women as compared with young men [5]. In addition, absence of available evidence-based guidelines for diagnosing and treating hypertension in this age group (18-29 years) may be responsible for the fact that the majority of the patients are not properly managed in this institution as well as a variety of practice venues. Given the lack of definitive guidelines in this age group, extensive laboratory testing for these patients is not surprising. Underutilization of recommended tests and overutilization of tests with limited usefulness (such as liver profiles and chest radiographs) have been reported in practice audits and surveys in hypertensive adults in other countries [11-14]. In this study, renal parenchymal hypertension was properly diagnosed following the results of the initial set of tests. However, the main problem was inflation of diagnostic efforts to identify a secondary cause other than renal parenchymal hypertension, especially renovascular etiology.

The results of the present study reveal that higher systolic and diastolic blood pressures were measured more frequently in patients with BMI ≥24 kg/m^2 than those with BMI<24 kg/m^2. Numerous population-based and clinical studies have documented a strong positive relationship between BMI and blood pressure [15,16]. Moreover, overweight, obesity, and weight gain have been shown to be important and independent risk factors for the development of hypertension [17-19]. Increased BMI is associated with insulin resistance [20], an independent, established contributor to the development of hypertension, like increased BMI [21]. Consequently, the more overweight or obese the person, the more likely these people are to be insulin-resistant with an increased risk of cardiovascular disease [22], including primary hypertension [23].

According to our study, it appears that the prevalance of secondary hypertension is less frequent in younger individuals with higher BMI values (≥24 kg/m^2). We believe that increased insulin resistance associated with increased BMI values might play an important role in this issue. Previously, it has been reported that the prevalence of insulin resistance/hyperinsulinemia is increased in patients with primary hypertension and insulin resistance/hyperinsulinemia have been shown in prospective studies to be independent predictors of the development of primary hypertension [21]. Therefore, patients with higher BMI values are prone to develop primary rather than secondary hypertension in this research is probably due to increased insulin resistance. However, we could not evaluate insulin resistance in this study. Confirming our hypothesis, Shamiss et al. showed that primary hypertensive patients had significantly lower insulin sensitivity than patients with hyperaldosteronism and renovascular hypertensive patients [24]. Their results suggest that secondary hypertension is not an insulin resistant state [24].

There are some limitations of the present study. The sample size is small and larger prospective studies are needed to develop a guideline for young adult hypertensives. A diagnostic guideline will be better derived from an analysis involving sensitivity and specificity of individual diagnostic tests, which cannot be evaluated given the retrospective design of the study. However, the results of the present work is significant because:

1. To our knowledge, this study is an important trial that evaluates the use of the diagnostic tests in a special hypertensive population, in the young adults. This is a clinically important time interval for it serves as a passage from childhood and adolescence, in which secondary causes of HT are more prevalent and considered by physicians, to adulthood, in which

more than 90% of cases the etiology is unknown or primary.

2. The present work demonstrated that a more aggressive approach in the evaluation of secondary causes of hypertension would not significantly benefit these patients unless there is a presence of several strong clinical clues suggestive of secondary hypertension, as stated in JNC VII [6], the 2007 guidelines of the European Society of Hypertension (ESH), and the European Society of Cardiology (ESC) [25].
3. The results of this work suggest that diagnostic tests used to identify a secondary cause for hypertension should be cautiously ordered in overweight and obese young adults without strong clinical clues suggestive of secondary hypertension.

In conclusion, when the remarkable prevalance of HT in this spesific population is taken into account, a simple stepwise diagnostic guideline can not only prevent inflation of diagnostic tests but would be of great benefit in the management of young hypertensive patients as well.

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