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Special Article

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Shifting from Pharmacotherapy to Prevention of Hypertension

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ABSTRACT

Hypertension is a common chronic disease affecting a large section of the general population. As hypertension is usually asymptomatic, awareness, treatment and control rates are low. Drug side-effects also affect compliance. Hypotension and electrolyte abnormalities in the elderly can be severe. Therefore, prevention is better than cure. As blood pressure rises with age, prevention should be started early. As there are many genes affecting blood pressure, genetic tests are not useful. Good antenatal care and care of preterm infants can help to prevent adult cardiovascular diseases including hypertension. Childhood obesity is an important determinant of blood pressure in childhood and adolescence. This is a window of opportunity for prevention. The current American College of Cardiology/American Heart Association guideline on hypertension defines stage 1 hypertension as a systolic blood pressure of 130–139 mmHg or a diastolic blood pressure of 80–89 mmHg. Although this makes many people in the general population hypertensive, stage 1 hypertension in young adults is already associated with increased cardiovascular and mortality risk. Fortunately, hypertension at this early stage is easy to control and weight loss is easier in young males, who can get exercise from work or exercise after work. Leisure-time physical activity seems more beneficial than occupational physical activity. Cardiovascular risk assessment and promoting a healthy lifestyle in the young are likely to forestall hypertension and future cardiovascular disease. Preventing or reversing hypertension is no longer an impossible dream.

Keywords: Hypertension; Drug therapy; Essential hypertension; Prehypertension; Primary prevention; Secondary prevention

INTRODUCTION

Hypertension is a chronic disease affecting a large proportion of the general population.[1)] About a third of adult Americans are hypertensive.[2)] In a large country such as China, there are a quarter of a billion adults with hypertension.[3)] In India, the prevalence is 33% in cities and 25% in rural areas.[4)] In South Korea, the prevalence is also around a third of adults.[5)] Hypertension is a major risk factor for coronary heart disease, strokes, heart failure and chronic kidney disease. Therefore, detecting and treating hypertension is a high priority and can reduce morbidity and mortality.

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Unfortunately, hypertension is often asymptomatic. This means that many people with hypertension are unaware of it and may not present to their doctors for diagnosis and treatment. Because of the asymptomatic nature and the fact that heart attacks and strokes occur in older adults, many younger patients with hypertension do not want to seek treatment, take regular medications and attend regular follow-ups. Therefore, the problem is more than just checking everybody's blood pressure, because there are barriers to overcome.

A large part of the problem is that antihypertensive treatment is not very user-friendly. Most antihypertensive drugs are far from perfect. They have limited effectiveness, have adverse side-effects (**Table 1**)[6] and need to be taken regularly. The limited efficacy of antihypertensive drugs partly stems from our lack of understanding of the pathogenesis of hypertension. In the vast majority of hypertensive patients, there is not a single cause, let alone a cause that can be removed upon treatment. In our current knowledge, blood pressure is controlled by multiple physiological systems, including the sympathetic nervous system, the renin-angiotensin system and the vascular endothelium (**Table 2**).[7] No wonder a drug that acts on a single system may not be sufficient to normalise the blood pressure in a hypertensive person. Most, if not all, antihypertensive drugs have side-effects (**Table 1**).[6] This limits the choice of drugs and also limits dosage as higher dosages may not be tolerated. Hence, beta-blockers and thiazide diuretics are to be used at low doses. Because of ankle oedema, higher doses of the calcium channel blocker amlodipine often cannot be tolerated. Adverse drug effects also impact on compliance. Adherence to antihypertensive drug regimens is known to be poor and this has been extensively studied.[8] Adverse effects of antihypertensive medications can sometimes be severe and life-threatening. Elderly hypertensive patients who are on multiple

Table 1. Common adverse effects of antihypertensive drugs

Drug class	Adverse effects
Alpha$_1$-adrenergic antagonist	Postural hypotension.
Angiotensin-converting enzyme inhibitors	Cough, hyperkalemia, angio-oedema, creatinine rise.
Angiotensin receptor blockers	Hyperkalemia, creatinine rise.
Beta-adrenergic blockers	Bradycardia, fatigue, heart block, bronchospasm, intermittent claudication, cold extremities.
Calcium channel blockers	Flushing, headache, constipation, peripheral oedema. Verapamil and diltiazem are negatively chronotropic and inotropic.
Diuretics, thiazide or thiazide-like	Hypokalemia, hyponatremia, hyperuricaemia, postural hypotension.
Potassium-sparing diuretics	Hyperkalemia, gynaecomastia caused by spironolactone.

Table 2. The major systems involved in blood pressure regulation

System	Effect on blood pressure regulation	Effect on blood pressure
Sympathetic nervous system	Catecholamine release ↑ Renal sympathetic activity ↑ Na^+ retention	↑
Renin-angiotensin-aldosterone system	↑ Na^+ reabsorption ↑ Aldosterone secretion Endothelial dysfunction Renal, cardiac and vascular injury	↑
Immune system	↑ Macrophage infiltration ↑ Na^+ sensitivity ↑ Pro-inflammatory T_H1 cells	↑
Natriuretic peptides	Natriuresis Diuresis Vasodilation	↓
Endothelium	Nitric oxide production Vasodilation	↓

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antihypertensive drugs at high doses can suffer from postural hypotension and falls, severe bradycardia as well as electrolyte abnormalities such as hyponatraemia and hypokalaemia.[9]

Prevention is better than cure. We do not have the means to cure hypertension in the great majority of patients. Can we try to prevent it? Is it preventable? The focus of this article is to discuss if hypertension is preventable, and if so, how it may be prevented.

IS HYPERTENSION PREVENTABLE?

Although the majority of hypertensive patients have primary hypertension, meaning that no single antecedent cause can be identified, a proportion of patients have secondary hypertension (**Table 3**).[10] In a hypertension referral clinic, these secondary causes are carefully considered and excluded. In patients presenting with hypertension at a young age,[11] or in patients with difficult-to-control hypertension, it is especially important to consider and look for these secondary causes. Conn's syndrome is recognized as one of the more common causes of secondary hypertension. Among patients with resistant hypertension, spironolactone has been found to be an effective drug,[12] prompting speculation that some patients with resistant hypertension may have Conn's syndrome. In recent years, there is much interest in the adrenal aldosterone-secreting adenomas.[13] To diagnose these at an early stage require the ^{11}C-metomidate positron emission tomography-computed tomography scan,[14] which is not yet widely available. These adenomas can be removed laparoscopic, so these patients potentially have a form of hypertension that is curable.

Table 3. Secondary causes of hypertension

Anatomical	Coarctation of the aorta
Renal	Renal artery stenosis
	Polycystic kidneys
	Glomerulonephritis
	Pyelonephritis
	Diabetic nephropathy
	Other causes of renal failure
Endocrine	Hyperaldosteronism (including Conn's syndrome)
	Phaeochromocytoma
	Cushing's syndrome
	Acromegaly
	Hyperparathyroidism
Respiratory	Obstructive sleep apnoea
Vasculitis	Systemic lupus erythematosus
	Polyarteritis nodosa
	Takayasu's disease
Medication	Corticosteroid
	Oral contraceptive
	Carbenoxolone
	Liquorice
	Cyclosporin
	Non-steroidal anti-inflammatory drugs
	Venlafaxine
	Pseudoephedrine
Substance of abuse	Amphetamines
	Cocaine
	Ephedra
	Alcohol

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There are a small number of conditions, such as Liddle syndrome, where the patient has a single gene disorder that causes hypertension.[15] However, single-gene disorders causing hypertension are rare. For the majority of patients, they may have a genetic predisposition to hypertension mediated by multiple genes. Over a hundred genes influencing blood pressure have been identified in genome-wide association studies.[16] It is therefore possible to construct a genetic score that gives an indication of the genetic predisposition to hypertension. Currently, such genetic tests are costly and have no clear clinical purpose.[15] For example, counselling and prenatal diagnosis are not warranted. After all, hypertension is not a life-threatening disease and is treatable. Moreover, the impact of genetics on blood pressure is small, accounting for several millimetres of mercury only.[16] Intrauterine growth has a role in the pathogenesis of hypertension according to Barker's hypothesis.[17] Therefore, good antenatal care has a bearing on metabolic syndrome and hypertension in later life. Work by Modi and colleagues also highlight the importance of good care of pre-term infants,[18] which may help to reduce the risk of developing later in life cardiovascular diseases, including hypertension.

Except in some rural populations, blood pressure tends to rise with age from the moment a child is born. In old age, concurrent with the rise in systolic blood pressure is a tendency for the diastolic blood pressure to decrease because of arterial stiffness.[19] This results in increased pulse pressure and also the phenomenon of isolated systolic hypertension. The trajectory of blood pressure is slightly different in men and women.[20] Young women have a much lower level of blood pressure than men of the same age but there is a steep rise in blood pressure around the time of menopause. As blood pressure rises with age, it means that the prevention of hypertension should be started at an early age before it becomes full-blown. This is a window of opportunity for the prevention of hypertension. Our own work suggests that childhood obesity is an important determinant of blood pressure in childhood and adolescence (**Figure 1**).[21] Both systolic and diastolic blood pressure vary directly with body mass index or waist circumference (**Figure 2**).

The relationship between blood pressure and obesity should not come as a surprise since hypertension and obesity are both components of the metabolic syndrome. The latter predicts not only the development of type 2 diabetes but also hypertension.[22] In a Mendelian

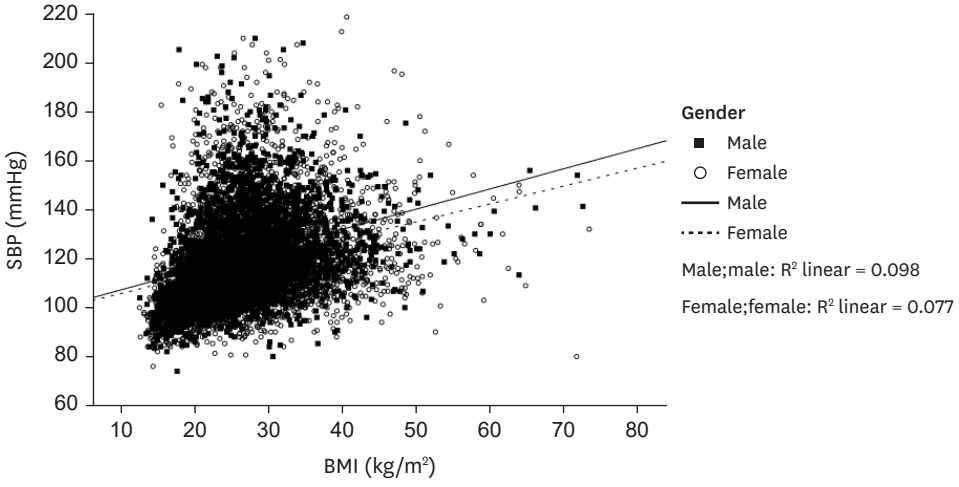

Figure 1. Relationship of systolic blood pressure with BMI and waist circumference.
BMI = body mass index; SBP = systolic blood pressure.

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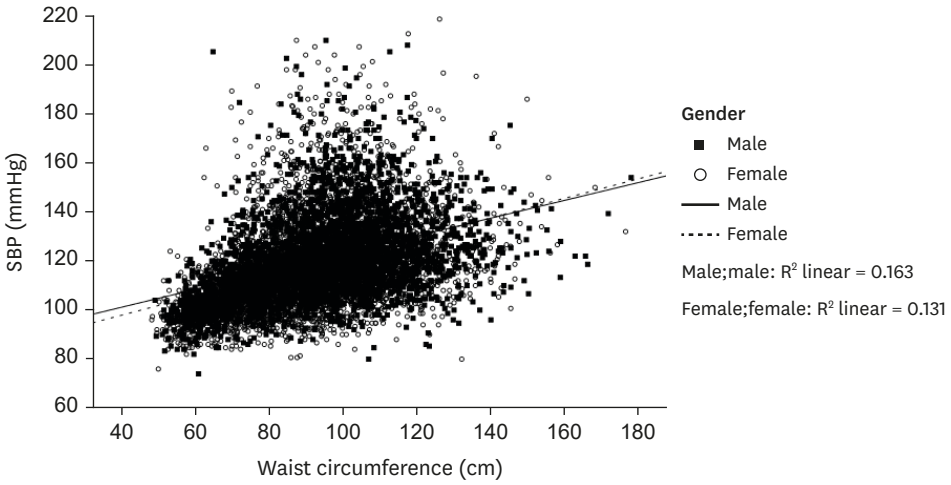

Figure 2. Data on 3,653 boys and 3,697 girls from National Health and Nutrition Examination Survey 2007–2008 are shown.[19]
The blood pressures of boys and girls are represented by filled squares and open circles, respectively. The regression lines for boys and girls are shown as full and broken lines.
SBP = systolic blood pressure.

randomisation study, genetic variants associated with obesity were used instead of body mass index (BMI), which is affected by environmental factors.[23] Those who carried genetic variants causing obesity tended to have higher blood pressure, providing strong evidence for a causal link between the two. Each 1 kg/m^2 increase in BMI increased the risk of hypertension by 19%. To complete the proof that obesity causes hypertension, one can look at studies of drugs that lower bodyweight. Orlistat,[24] glucagon-like peptide 1 (GLP-1) receptor agonists[25] and sodium-glucose cotransporter-2 (SGLT-2) inhibitors[26] all lower blood pressure along with a decrease in body weight. GLP-1 receptor agonists and SGLT-2 inhibitors, which are primarily used for the treatment of type 2 diabetes mellitus, have the additional advantage of reducing cardiovascular events.[27] In case there is doubt that these drugs have a pleiotropic effect on blood pressure, a meta-analysis of bariatric surgery, which is non-pharmacological, showed a marked reduction in the risk of hypertension.[28]

There is now a global epidemic of childhood obesity.[29] It is a problem of rich countries such as the USA, but also afflicts low-income countries. Poverty leads to consumption of calorie-dense foods with high glycaemic indices.[30] Combating childhood obesity should be high on the agenda because if unchecked, there will be in store for the future epidemics of not only hypertension, but also type 2 diabetes and coronary heart disease.[31]

EARLY-STAGE HYPERTENSION

The 2017 American College of Cardiology/American Heart Association (ACC/AHA) guideline on the prevention, detection, evaluation and management of high blood pressure controversially redefines the thresholds for diagnosing hypertension (**Table 4**).[32] The new definition of stage 1 hypertension includes people with a systolic blood pressure of 130–139 mmHg or a diastolic blood pressure of 80–89 mmHg. At a stroke, this increases the prevalence of hypertension in the general population[33] and turns a lot of asymptomatic people in the general population into hypertensive individuals. This has been criticized for unnecessarily labelling people with a medical diagnosis,[34] when most of them just need to lose weight and exercise more.

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Table 4. Categories of blood pressure in adults in the 2017 ACC/AHA guideline

Blood pressure categories	Systolic blood pressure		Diastolic blood pressure
Normal	<120 mmHg	and	<80 mmHg
Elevated	120–129 mmHg	and	<80 mmHg
Hypertension			
Stage 1	130–139 mmHg	or	80–89 mmHg
Stage 2	≥140 mmHg	or	≥90 mmHg

Individuals with systolic blood pressure and diastolic blood pressure in two categories should be designated to the higher blood pressure category.
Blood pressure record should be obtained based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in Section 4 of the 2017 ACC/AHA guideline.[30]
ACC/AHA = American College of Cardiology/American Heart Association.

Studies in Koreans as well as Americans suggest that stage 1 hypertension in young adults is already associated with increased cardiovascular events and mortality.[35][36] Therefore, tackling stage 1 hypertension in young adults is not without reason, although the cost-effectiveness of different treatment options needs to be defined. Lifestyle treatment is likely to be cost-effective since it involves little cost to the public health system or the medical insurance.

We have studied the characteristics of people with stage 1 hypertension in the United States National Health and Nutrition Examination Survey and found that most of them are male and obese without any history of cardiovascular disease yet (**Table 5**).[37] Therefore, the ACC/AHA guideline recommendation of lifestyle modification for these individuals seem very appropriate.

HOW TO PREVENT HYPERTENSION?

There is a difference between the approach to diagnosing and treating hypertension in young and old people. In young people, hypertension is often undiagnosed, but blood pressure control can usually be achieved easily. In contrast, awareness of hypertension is high in the elderly, but blood pressure is often difficult to control, resulting in a low control rate.[38]

Table 5. Characteristics of adult participants with stage 1 hypertension in National Health and Nutrition Examination Survey 2015–2016

Characteristic	Not on anti-hypertensive medication	On anti-hypertensive medication
Number	558	396
Age (years)	46.35±19.61	57.89±16.91
20–39 (%)	36.62 (31.67–41.78)	11.27 (8.29–15.14)
40–59 (%)	44.22 (37.66–50.92)	39.74 (32.47–47.48)
≥60 (%)	19.17 (14.61–24.43)	49.00 (41.73–56.31)
Female (%)	44.03 (40.04–48.08)	48.59 (40.89–56.36)
Systolic blood pressure (mmHg)	128.98±9.69	131.78±7.96
Diastolic blood pressure (mmHg)	77.04±17.24	72.60±19.51
Body mass index (kg/m^2)	30.16±7.56	31.58±8.36
Waist circumference (cm)	102.39±19.37	106.57±24.87
Abdominal obesity US cut-offs (%)*	62.76 (54.64–70.38)	73.78 (66.82–79.72)
Abdominal obesity IDF cut-offs (%)†	79.70 (75.75–83.27)	89.60 (83.50–93.61)
History of cardiovascular disease (%)	2.31 (1.48–3.42)	14.45 (8.92–22.57)
Diabetes mellitus (%)	2.46 (1.31–4.18)	3.67 (2.06–6.44)
Cigarette smoking (%)	16.82 (12.07–22.52)	18.30 (12.99–25.15)

Data are shown as mean±standard deviation. For percentages, the 95% confidence intervals are shown.
IDF = International Diabetic Federation.
*Abdominal obesity is defined as ≥102 cm and ≥88 cm for male and female, respectively. †Abdominal obesity is defined as ≥94 cm and ≥80 cm for male and female, respectively.

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Table 6. Comparison of prevention with treating only the sick

	Prevention	Treating the sick
Scale	Large population	Targeted
Costs	Cost per person low	Cost per person high
Infrastructure	Non-specialist	Trained personnel or specialist
Outcome	Superior	Inferior

Stage 1 hypertension should therefore be easy to control. Most of these patients do not require drug treatment.[33] Exercise is easier for young males, who are more likely to have enough physical activity either at work or after work. In the retired elderly, they have fewer opportunities to have enough physical activity, and their exercise capacity might be limited by comorbidities and mobility problems. Leisure-time physical activity seems to be more beneficial than occupational physical activity.[39] Therefore, current recommendations from the World Health Organisation and the American US Physical Activity Guidelines US Department of Health and Human Services (of exercising at least 150 minutes a week are highly appropriate.[40]

There are a number of new and experimental treatments for hypertension that do not involve drugs, such as renal denervation,[41] splanchnic denervation,[42] central iliac arteriovenous anastomosis,[43] vaccine[44] and gene therapy.[45] Rather than curing or preventing hypertension, these technological advances are primarily aimed at patients with resistant hypertension who do not tolerate conventional drug therapy well. As most people in the general population are at risk from hypertension, especially when they live to a ripe old age, the approach to the prevention of hypertension must be safe and economical (**Table 6**). Lifestyle modification fits the bill very well.

CONCLUSIONS

While detecting and adequately treating hypertension remain important goals in the management of hypertension, the prospect of preventing hypertension is very attractive.

Cardiovascular risk assessment and promoting a healthy lifestyle in the young are likely to forestall hypertension and future cardiovascular disease.

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