Hypertension: Is It Time to Replace Drugs With Nutrition and Nutraceuticals?

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The October, November, and December 2013 issues of the *Journal of Clinical Hypertension* (a conservative and traditional medical journal) each included a section of a major research review article on a topic that hard-science, data-driven clinicians might not have taken seriously until recently. The topic under consideration: replacing antihypertensive medications with appropriate nutrition and nutraceutical supplements.[1]

In an interview, article author Mark Houston, MD, commended the open-mindedness of *Journal of Clinical Hypertension* Editor-in-Chief Michael A. Weber, MD. The article's reception has for the most part been highly positive, Dr. Houston added.

"People's eyes have been opened," he said. There has been some amazement at how much science is in the literature to back up such strategies, he added, and surprise about the extent to which hypertension patients are clamoring to know more about ways to avoid or reduce the polypharmacy offered by conventional practitioners.

Dr. Houston has triple board certification. He is certified as a hypertension specialist by the American Society of Hypertension and is a fellow of the society. He is board certified as well in internal medicine (by the American Board of Internal Medicine) and anti-aging medicine (by the American Board of Anti-Aging/Regenerative Medicine). He also is a functional medicine practitioner, certified by the Institute for Functional Medicine. Following this certification he completed two master of science degrees, one in nutrition and the other in metabolic medicine. He is an Associate Clinical Professor of Medicine at Vanderbilt University School of Medicine, and Director of the Hypertension Institute, Vascular Biology, and Life Extension Institute and Medical Director of the Division of Human Nutrition at Saint Thomas Medical Group, Nashville, Tennessee.

Functional medicine practitioners, aware of the increase in complex, chronic diseases such as diabetes, heart disease, hypertension, cancer, mental illness, and autoimmune disorders, focus on identifying the underlying causes of disease and look for interactions between genetic, environmental, and lifestyle factors. They seek to promote health and vitality by integrating conventional practices with prevention through combinations of drugs and/or botanical medicines, supplements, therapeutic diets, detoxification, exercise, and stress management rather than emphasizing acute symptom relief, urgent care, and elimination of illness and disease.

Hypertension

The most recent National Health and Nutrition Examination Survey figures report U.S.-born adults' hypertension control rate, although improving, still hovered below 50% in 2010. At the same time, millions of Americans have been turning to alternative and complementary therapies along with dietary supplements as substitutes or add-ons to conventional multidrug pharmacological therapy for hypertension, a variety of other maladies, and general health support.

In a February 2014 presentation at the Integrative Healthcare Symposium 2014 in New York City, Dr. Houston reaffirmed the *Journal of Clinical Hypertension* paper's message that a diet- and supplement-based strategy in combination with appropriate lifestyle change can sometimes, but not always, replace a pharmaceutical-based approach to treating hypertension and preventing target organ damage.

Definitions at Odds

The Mayo Clinic website defines hypertension as "a common condition in which the force of the blood against your artery walls is high enough that it may eventually cause health problems, such as heart disease."[2] Dr. Houston reframes the issue, positing that hypertension is a "correct and chronic dysregulated vascular response to infinite insults to the blood vessel. The exaggerated initial outcome of these insults is finite and threefold: inflammation, oxidative stress, and vascular immune dysfunction. Their further consequences, both biomechanical and biohumoral (biochemical, metabolic, and nutritional), are vascular damage, and endothelial and vascular smooth muscle dysfunction with vasoconstriction and hypertension." The vascular system in this interplay with environmental-gene expression patterns is an innocent bystander, according to Dr. Houston. Elevated blood pressure is one among multiple responses to endothelial dysfunction and vascular smooth muscle dysfunction, both of which precede the development of hypertension by decades.

While recognizing the role of genetic predisposition, Dr. Houston emphasized the major role of environment. "Eighty percent of vascular disease is environmental. It is not genetic … so it's important to tell this to your patients so they don't feel that they are doomed to have a cardiovascular event if there's a family history." The key to prevention and treatment of hypertension and cardiovascular disease, then, is in modulation of the environmental insults and the downstream disturbances of gene expression patterns.

The two major players in vascular disease leading to hypertension are angiotensin II and nitric oxide. When chronically elevated, angiotensin II promotes excessive vasoconstriction and hypertension, inflammation, oxidative stress, vascular immune dysfunction, thrombosis, and growth. It is also proatherogenic. Nitric oxide, its antithesis, causes vasodilation, is antihypertensive and anti-inflammatory, and reduces oxidative stress, vascular immune dysfunction, and thrombosis. It is antiatherogenic. Therapeutic strategies, through either pharmacological agents or nutrients, would therefore aim at increasing nitric oxide availability and decreasing the effects of angiotensin II.

As to the question "Which occurs first, the vascular disease or the hypertension?" most people now believe that the microvascular disease and the endothelial dysfunction occur first, Dr. Houston said, with the blood pressure as a marker. But once

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the blood pressure goes up, it causes more endothelial dysfunction. It is clearly then bidirectional, so both have to be treated at the same time in an integrative approach that improves vascular health, optimizes vascular biological function and structure, and slows vascular aging and subsequent cardiovascular disease.

Pathophysiology

The components of hypertension's pathophysiology include oxidative stress, inflammation, and autoimmune dysfunction. Reactive oxygen and nitrogen species levels become higher in the arteries and kidneys, while oxidative defenses are decreased.

Inflammation is increased in the vasculature and kidneys through greater levels of high-sensitivity C-reactive protein (Hs-CRP), leukocytosis, increased neutrophils, and reduced lymphocytes. In the kidney, renin-angiotensin-aldosterone system activity is heightened. Also in the arteries and kidneys, autoimmune destruction is attended by increased white blood cells and involvement of T-helper cells and cytotoxic T cells (CD4+/CD8+). "If you couple this with genetics, epigenetics, and environmental-genomic interactions, then you have the inflammatory fire, the volcano in your arteries, and your heart ready to erupt at any time."

Hs-CRP is both a risk marker and risk factor for hypertension and cardiovascular disease. The angiotensin type 1 receptor (AT1R) when stimulated is known to be inflammatory and to increase oxidative stress, vascular immune dysfunction, and hypertension. It is counterbalanced by the angiotensin type 2 receptor (AT2R). Hs-CRP inhibits endothelial nitric oxide synthase and reduces nitric oxide, down-regulating the AT2R.[3]

The induced vascular immune dysfunction feeds the same cycle, with vascular injury attracting monocytes, macrophages, and CD4+ T lymphocytes, leading to release of pro-inflammatory mediators, tumor necrosis factor alpha, interferon, and interleukins (especially IL-17), building on the cascade of angiotensin II–based hypertension genesis events.

It has only recently been recognized, Dr. Houston pointed out, that aldosterone is an immune stimulant.[4] Angiotensin II can induce hyperaldosteronism, and more than 30 inflammatory genes are produced just through the effects of aldosterone. Blockade of aldosterone, even with persisting hypertension or in normotensive patients, reduces cardiovascular risk.

Considering genetics and epigenetics, Dr. Houston noted that most of the single-nucleotide polymorphisms (SNPs) related to hypertension and cardiovascular disease are associated with oxidative stress, inflammation, and immune dysfunction. An analysis of a microarray of genetic polymorphisms in hypertension showed most of them (31 of 49) to be up-regulated to an inflammatory process.[5] Coronary disease, too, is correlated with inflammatory up-regulation, more so than with what are considered to be the top five coronary disease risk factors (hypertension, dyslipidemia, hyperglycemia, smoking, and obesity).

The new treatment approach, Dr. Houston said, views hypertension as a disease in which the vascular biology is altered and the arteries need to be treated appropriately through nonpharmacological mechanisms: nutrition, nutraceutical supplements, antioxidants, weight loss, exercise, meditation, and sleep. Then the pharmacological approach can be integrated to achieve the maximum reduction and protection of the cardiovascular system. The preferred drugs are angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), and calcium-channel blockers (CCBs). Dr. Houston, in general, does not recommend beta blockers, diuretics, central alpha agonists, or alpha blockers. "But if you change the lifestyle and give it some time, eventually you probably can get [patients] off many of the drugs."

The guidelines of the Joint National Commission on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC), Dr. Houston noted, have provided a nonmechanistic, nonpersonalized approach to treating hypertension; the same strategy is applied generally to all patients. About a decade ago, Dr. Houston and colleagues began stratifying patients according to plasma renin activity (PRA), as advocated by John Laragh, MD, for about half a century, and aldosterone levels. Plasma renin is the enzyme that leads to angiotensin II. Those with elevated angiotensin II levels generally have elevated PRA. High renin hypertension (PRA greater than 0.65 ng/mL an hour, about 70% of patients) is associated with decreased intravascular volume and higher risk for myocardial infarction (MI), ischemic heart disease, stroke, congestive heart failure, chronic kidney disease, and cardiovascular and overall mortality.[6,7] Renin drugs (ACEIs, ARBs, direct renin inhibitors, beta blockers, and central alpha agonists) and nutraceuticals are recommended for this population. Low renin hypertension (PRA less than 0.65 ng/mL per hour, about 30% of patients), associated with increased intravascular volume, is treated with volume drugs (CCBs, diuretics, serum aldosterone receptor antagonists such as spironolactone and eplerenone, and alpha blockers) and nutraceuticals.

Diagnosis

Standard blood pressure measurements, because they often do not accurately reflect cardiovascular health, can be misleading and are likely to become obsolete, Dr. Houston said. The ability to noninvasively measure blood pressure in central arteries is an important advance because the central and brachial pressures do not always correlate. For example, Dr. Houston said, while the blood pressure measured brachially in a sitting patient receiving a beta blocker may be normal (120/80 mm Hg), the central pressure can be as much as 10 mm Hg higher, with the patient remaining at significant risk, as demonstrated in the CAFÉ trial (the Conduit Artery Functional Endpoint Study).[8]

But measuring central pressure still gives only one point in time. The new standard is 24-hour ambulatory blood pressure monitoring (ABPM) that simultaneously measures the brachial pressure and the central pressure in the aorta. It is standard of care in the United Kingdom but not in the U.S.; coding "white coat" or "labile" or occasionally "resistant" hypertension will elicit insurance approvals, Dr. Houston said.

Twenty-four hour ABPM is superior to home and office blood pressure monitoring for predicting future cardiovascular events and target organ damage.[9] It has been shown to reduce by 25% the number of patients needing drug therapy, and overall it has been shown to be cost effective.

Twenty-four hour ABPM reveals important parameters missed by brachial readings, including nocturnal blood pressure, dipping status, white coat and masked hypertension, circadian rhythms with the early morning surges known to be associated with cardiovascular events and strokes, load (the

percentage of reading greater than 140/90 mm Hg), and blood pressure highs, lows, and variability. Nocturnal blood pressure predicts event risk much better than daytime pressures.

In healthy normotensive individuals, nocturnal blood pressure reductions are 27/15 mm Hg lower than daytime readings. Cardiovascular risk is higher with over- and under-dipping by more than 10%. Excessive dipping (more than 20%) increases ischemic stroke risk, while reverse dipping (0–20%) increases hemorrhagic stroke risk.

Nondipping does not allow renal sodium excretion and is most common in sodium-sensitive patients and African Americans.[10–12] It is more likely to be found as well in patients with renal insufficiency, secondary forms of hypertension, diabetes, cerebral volume loss, cognitive impairment, left ventricular hypertrophy, refractory hypertension, obstructive sleep apnea, and autonomic dysfunction. Nondipping is highly correlated with coronary heart disease (CHD), cardiovascular disease, congestive heart failure, chronic renal failure, increased carotid intima media thickness, multifocal leukoencephalopathy, and silent cerebral infarctions.

Treatment

Event rates are strongly affected by timing of treatment administration; they are 25% to 50% lower when a drug is given at night. Also, most drugs may partially convert nondippers to dippers if dosed nocturnally. The drugs that will *not* convert nondippers are those recommended, Dr. Houston emphasized, by JNC reports 1 through 8: thiazide diuretics (hydrochlorothiazide), thiazide-like diuretics (chlorthalidone), and the older beta blockers like metoprolol and most other "ols." The ones that will convert nondippers are ACEIs, ARBs, most CCBs, and perhaps one or two newer beta blockers (nebivolol and carvedilol).

Dr. Houston noted that he is aware of only one supplement that has been studied that will convert nondippers to dippers, and that is melatonin at nocturnal doses of 3 to 4 mg at night.

Nocturnal Hypertension

Nocturnal hypertension, defined as nighttime blood pressure greater than 120/70 mm Hg, is more common than nondipping and is found in about 70% of hypertensive patients.[13–15] It is a more powerful predictor of cardiovascular morbidity and mortality than circadian, mean, or daytime blood pressure. Among patients with nocturnal hypertension, dosing at night with a dipping status–converting drug (ACEI, ARB, CCB, nebivolol[16]) reduces events by 29% to 38%.

The JNC-recommended hydrochlorothiazide and older beta blockers are less effective at reducing central blood pressure. The CAFÉ study indicated that these agents may reduce brachial pressure while leaving centrally measured systolic blood pressure unchanged or higher (by 4.3 mm Hg). At the same time, central aortic pulse pressure was 3.0 mg higher due to pulse wave augmentation. Central blood pressure is more predictive than brachial pressure with respect to cardiovascular disease, cardiovascular disease mortality, all-cause mortality, and left ventricular dysfunction.

Returning to diuretics, Dr. Houston said that beyond failing to reduce central arterial pressure or to improve vascular function, microvascular structure, vascular remodeling, or hypertrophy compared with ACEIs, ARBs, and CCBs, they do not optimally reduce CHD or MI. The reductions in stroke and MI are 25% lower. JNC 8 still lists diuretics as Step I therapy. "I'm not sure why we are still recommending thiazide diuretics or older beta blockers for hypertension with the amount of contrary data[17,18] that has been published in major hypertension journals all over the world," he said.

If a diuretic *is* needed, among the comparative benefits with indapamide are better blood pressure control, 50% less hypokalemia, minimal to no hyperglycemia or insulin resistance, lipid neutrality, less microalbuminuria, renal benefits, and better cardiac effects.[17,19] Chlorthalidone is an alternative to hydrochlorothiazide that offers better cardiovascular outcomes and longer duration of action, but is not as good as indapamide with respect to all the other metabolic effects and cardiovascular disease outcome data, Dr. Houston said.

Similarly, rates of adverse effects are high with first- and second-generation beta blockers, while refill and compliance rates are low. More favorable brachial and central blood pressure, augmentation index, pulse wave velocity, endothelial dysfunction, systemic vascular resistance, nitric oxide, antioxidant, and other vascular and metabolic effects make nebivolol and carvedilol preferable.

"The only time I use beta blockers now is in the post–myocardial infarction patient, the patient who has congestive heart failure (either systolic or diastolic) or who has an arrhythmia-like supraventricular tachycardia or premature ventricular contractions. In hypertension, beta blockers are less effective in reducing central blood pressure, coronary heart disease, MI, and overall cardiovascular mortality compared to ACE inhibitors, ARBs, CCBs, or these in combination—and they really make you feel bad," Dr. Houston said. CCBs are very good for reducing blood pressure and for reducing strokes at the same blood pressure level compared to any other class (by 10% more).

Nutrient Testing

By looking at nutritional correlations to vascular disease and hypertension and by performing a nutritional analysis on specific patients, a program that addresses nutritional deficiencies with vitamins, antioxidants, minerals, and nutraceutical supplements can be initiated.

Every patient who comes to Dr. Houston's office gets an intracellular lymphocyte analysis, a six-month functional assay of a patient's nutrients. It reveals what that lymphocyte is deficient in, and how much replacement would be required to make it work better. The most accurate assay, Dr. Houston said, is available only through SpectraCell Laboratories (Houston, Texas), and is covered by some insurance plans. Typically many patients become normotensive by counterbalancing their nutritional and supplement deficiencies within three to six months.

The Hypertension Institute engages a full-time licensed nutritionist, exercise physiologist, and personal trainer who sees and advises all patients. Information on relaxation and stress-reducing meditation is also provided. "It's an extremely important part of what we do in cardiovascular medicine," Dr. Houston said.

The recommended diet is essentially a Mediterranean diet with some modification: a lot of vegetables, some fruit, minimal to no carbohydrates, high-quality organic protein, and the right types of fats (primarily omega-3 fatty acids, monounsaturated fats, limited saturated fats, and no trans fats).