CASE REPORT

Hypertension

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ABSTRACT
Hypertension is responsible for roughly one-in-six adult deaths annually in the United States and is associated with five of the top nine causes of death.[1] Ten trillion dollars is the estimated annual cost worldwide of the direct and indirect effects of hypertension.[2,3] In the U.S. alone, costs estimated at almost $74 billion in 2009 placed a huge economic burden on the health care system.[4] The prevalence of hypertension increases with advancing age to the point where more than half of people 60 to 69 years of age and at least three-fourths of those 70 years of age and older are affected.[5] Most individuals with hypertension do not have it adequately controlled.[1,6] Medication noncompliance due to avoidance of side effects is suggested to be a primary factor.[6] The epidemic incidence of hypertension and its significant cost to society indicate that a well-tolerated, cost-effective approach to treatment is urgently needed.

摘要
在美国，每年大约有六分之一的成年人死于高血压。高血压在九大致死原因中排名第五。[1] 每年高血压在全世界直接和间接导致的费用估计为十万亿美元。[2、3] 单就美国而言，估计 2009 年费用约为 740 亿美元，这对医疗系统造成了沉重的经济负担。[4] 高血压的患病率随年龄增大而提高，60 至 69 岁的人群中有超过半数的人受到影响，而 70 岁及以上的人群中至少有四分之三的人受到影响。[5] 大多数高血压患者并未得到足够的控制。[1、6] 为避免副作用而用药不合规被认为是一项主要因素。[6] 高血压的发病率高，使社会承受着高昂的成本负担，因此亟需一种耐受性好且具成本效益的方法进行治疗。

SINOPSIS
La hipertensión es responsable de aproximadamente una de cada seis muertes en adultos anualmente en los Estados Unidos y está relacionada con cinco de las nueve causas de muerte más importantes.[1] Los efectos directos e indirectos de la hipertensión causan mundialmente un coste anual estimado de unos diez billones de dólares.[2,3] Solamente en los EE.UU., los costes estimados de casi 74.000 millones de dólares en el 2009 fueron un lastre económico enorme en el sistema de salud.[4] La prevalencia de la hipertensión se incrementa con la edad hasta el punto de que más de la mitad de las personas entre 60 y 69 años y al menos tres cuartos de las personas de 70 o más años de edad padecen se ven afectadas.[5] La mayoría de las personas con hipertensión no la controlan adecuadamente.[1,6] El incumplimiento de la medicación por motivo de los efectos secundarios es probablemente un factor principal.[6] La incidencia epidémica de la hipertensión y sus costes considerables para la sociedad indican que se necesita urgentemente un tratamiento con un enfoque rentable y bien tolerado.

CASE HISTORY

JF was 48 when he presented with a history of pharmaceutically managed hypertension. His goal was to decrease his medications, as he felt they were adversely affecting his quality of life. He experienced erectile dysfunction (ED), which he felt was exacerbated by the medication. He also complained of other medication-related side effects, including dizziness, fatigue, and general weakness. A little over ten years earlier, during a routine office visit, JF's physician discovered a blood pressure of 147/95 mmHg; the patient chose not to be concerned about blood pressure at that time, as he felt fine. However, ten years later, JF was not feeling well and was under a great deal of stress. He was also taking a number of "herbal stimulants," which he later discontinued. He visited his doctor, who found his blood pressure to be 250/160 mmHg. JF was immediately hospitalized for hypertensive crisis, complicated by diastolic dysfunction and congestive heart failure. The initial hospital treatment included diuresis with furosemide. His doctor then initiated triple antihypertensive therapy including a combination calcium channel blocker/angiotensin receptor blocker (amlodipine and olmesartan medoxomil 20 mg/40 mg) and 40 mg of extended release carvedilol, a non-selective beta blocker. Since a follow-up echocardiogram demonstrated improvement in diastolic dysfunction and hypertension, JF and his physician discontinued furosemide treatment. However, he remained on the three other blood pressure medications. It was at this time that JF sought the care of an integrative physician to support him in finding alternative options for

controlling his hypertension.

Additional history revealed that the patient had all but four of his dental amalgam fillings removed just prior to the hypertensive crisis. JF also had a history of multiple root canals for abscesses that resulted from dental caries. He was 35 pounds overweight. Though yoga was his main form of exercise, he did it intermittently. He reported his stress level to be 3 out of 10 (0 as lowest stress level possible, 10 as highest stress level possible) at the time of his visit. He took a variety of supplements; including vitamin E, fish oil, CoQ10, and magnesium citrate. His diet included a good deal of simple carbohydrate foods, such as white rice, potato and pasta, with some sweets.

JF's family history included a father who was a heavy smoker, deceased at age 50 from myocardial infarction, and a 76-year-old mother who had hypertension. He had two healthy sisters and one 53-year-old brother with hypertension (medicated) and coronary artery disease, status post stent placement.

JF's blood pressure was 162/104.

Initial Laboratory Results

Laboratory tests ordered and rationale:

1. **ADMA and arginine:** Evaluation of nitric oxide inhibition (ADMA) and nitric oxide substrate availability (arginine) Imbalances of both have been associated with hypertension.
2. **Urinary organic acids:** In this case, the organic acid profile was used to evaluate oxidative stress and inflammation.
3. **Lipid panel with fasting insulin and hsCRP:** Evaluation of metabolic imbalances and inflammation associated with cardiovascular disease
4. **Fat-soluble vitamins E and D, and CoQ10:** Nutrients required for cardiovascular function.

48-Year-Old Male with Resistant Hypertension on Triple Therapy

Symptoms and Conditions	Recent past history of hypertensive crisis, complicated by diastolic dysfunction and congestive heart failure; significant medication side effects, including weakness, fatigue, erectile dysfunction and dizziness
Medications	Amlodipine and olmesartan (Azor®); carvedilol (Coreg CR®)
Tests Used	Asymmetric dimethylarginine (ADMA), high sensitivity C-reactive protein (hsCRP), 8-hydroxy-2-deoxyguanosine (8-OHdG), quinolinate, red blood cell magnesium, vitamin D
Imbalances Identified	Elevated ADMA, hsCRP, 8-OHdG, and quinolinate; low red blood cell magnesium; low serum vitamin D
Treatments	Arginine, ascorbic acid, magnesium, and vitamin D; dietary and exercise modifications
Outcome	Decreased mean systolic and diastolic blood pressure from 162/104 to 130/85 over four months, allowing for a reduction in his antihypertensive medications to tolerable dosages that did not invoke side effects; 25 pound weight loss.
Discussion and Significance	Evidence suggests, and this case demonstrates, that effective, well-tolerated, non-pharmacological approaches to hypertension are available.[4,7] In this case, laboratory analysis was used to identify the underlying metabolic imbalances contributing to the patient's hypertension. The findings enabled the development of a personalized treatment protocol that was effective in reducing the patient's blood pressure to safer levels. The treatment allowed for a medication reduction that was sufficient to eliminate the side effects the patient had been experiencing. Because of the potential for significant improvements in morbidity, mortality and cost savings with the approach employed in this case, further research is warranted.

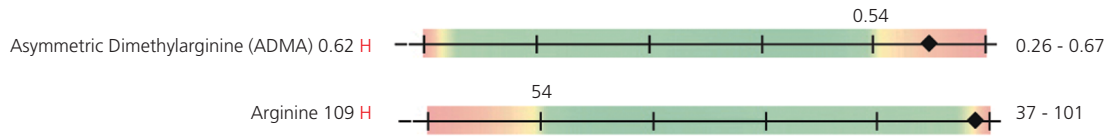

Figure 1 ADMA and arginine. Result showed a fifth quintile elevation of both plasma ADMA and arginine. (Units: µmol/L).

Figure 2 Inflammation. Results showed a significant elevation of hsCRP. The urinary organic acid quinolinate was high-normal in the fifth quintile. (Quinolinate units: µg/mg creatinine).

Figure 3 Oxidative stress. The urinary organic acid 8-OHdG was significantly elevated. (Units: ng/mg creatinine).

Figure 4 Red blood cell magnesium. The magnesium level was suboptimal.

Figure 5 Cardiovascular markers. Findings indicated hypertriglyceridemia with low HDL; insulin and total cholesterol were within normal limits.

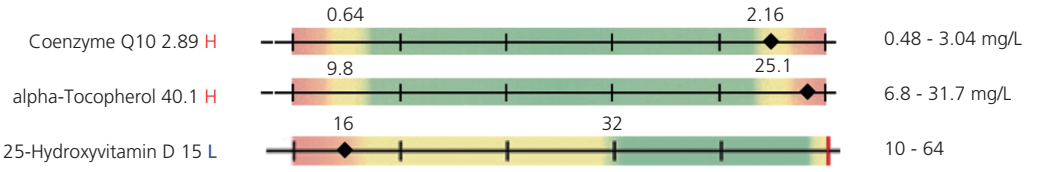

Figure 6 Fat-soluble nutrients. Elevated serum CoQ10, elevated vitamin E, and low vitamin D. (CoQ10 and vitamin E units: mg/L; vitamin D units: ng/mL)

Initial Assessment

- Hypertension (elevated ADMA and arginine)
- Congestive heart failure
- Hypertriglyceridemia
- Erectile dysfunction
- High triglyceride/HDL ratio suggests insulin resistance
- Hypomagnesemia
- Hypovitaminosis D
- Oxidative stress (elevated 8OHdG)
- Systemic inflammation (elevated hs-CRP and quinolinate)
- Periodontal disease

Initial Plan

- Titrate magnesium citrate up slowly to bowel tolerance
- Sustained release arginine: begin with 500 mg a day, and gradually increase to 3000 mg a day, in divided doses; begin after magnesium dosage stabilization
- Calcium ascorbate with bioflavonoids, 2000 mg a day for oxidative stress
- Vitamin D_3, 4000 IU per day for 3 months
- Oral irrigation daily (for periodontal disease)
- 1/2 tsp of cinnamon powder daily
- Low glycemic-index DASH diet (Dietary Approaches to Stop Hypertension)
- Decrease supplemental vitamin E
- Continue fish oil (essential fatty acids)
- Exercise program
- Recheck hsCRP and 8OHdG in 8 weeks
- Recheck vitamin D_3 in 3 months; goal > 55 ng/mL

Treatment plan rationale: The high ADMA level may have contributed to a relative arginine deficiency (despite an elevated plasma arginine finding) resulting in reduced nitric oxide availability that contributed to hypertension. Therefore, arginine supplementation was initiated. Magnesium was also needed, as indicated by the low RBC finding, which has specifically been associated with hypertension.[8] Ascorbate and bioflavonoids were introduced for their cardiovascular-protective, antioxidant and anti-inflammatory potential.[9, 10]

Vitamin D was initiated based on the laboratory finding. Hypovitaminosis D is associated with hypertension, inflammation and increased oxidative stress.[11] JF was advised to begin oral irrigation, given his history of periodontal disease. Cinnamon was recommended because it has been shown to help diminish insulin sensitivity and to have antimicrobial properties that would further support the treatment of periodontal disease.[12] A sugar-free, low glycemic-index (DASH-type) diet with exercise was also prescribed for insulin resistance. Despite elevated serum levels, CoQ10 was continued because it is nontoxic at higher levels and may be beneficial.[13] However, since vitamin E supplementation has mixed safety reviews in the literature, his self-prescribed dosage was reduced based on the elevated finding.[14, 15] It was recommended he continue fish oil for vascular disease risk reduction.[16]

One-Month Follow-up

JF's average blood pressure was 141/93. He was following the dietary suggestions, taking supplements as directed and had initiated exercise. He was pleased to report a five pound weight loss. It was suggested he reduce the amlodipine/olmesartan combination to 10 mg/20 mg per day and the carvedilol from 50 mg twice per day to 25 mg in the morning and 12.5 mg in evening. He was otherwise advised to continue the plan as directed.

Four-Month Follow-up

JF's average blood pressure was 130/85. He was following all aspects of his plan as prescribed. He stated

that he felt calmer, and was now walking daily and biking 3 to 4 days a week. His weight loss was at 25 pounds. He noted improvement with ED. He was very pleased with his progress, and was motivated to continue to improve. He was advised to remain on the amlodipine/olmesartan dose of 10 mg/20 mg and reduce the carvedilol to 12.5 mg once in the morning (at which dose he had no side effects). No other changes were made to his plan.

DISCUSSION

Hypertension is directly or indirectly associated with five of the top nine causes of death in the U.S., including heart disease, cerebrovascular disease, diabetes, renal disease, and essential hypertension.[1] Lifestyle risk factors play a significant role in hypertension etiology, including poor diet and nutrition, imbalanced salt and potassium intake, inactivity, and smoking. There is also a recognized genetic component.[1] Essential element deficiency, in particular that of magnesium, is strongly implicated as a contributing factor (Table 1).[17,18]

The patient had multiple imbalances that can contribute to hypertension, including an elevated ADMA (Figure 1). ADMA has been shown to impair nitric oxide function, and therefore has adverse effects on blood pressure, erectile function, and other nitric oxide–dependent activities.[19,20] Treatment with arginine and N-acetylcysteine has been shown to reduce both systolic and diastolic mean arterial blood pressure, total cholesterol, oxidized LDL, and high-sensitivity C-reactive protein.[21] ADMA synthesis, clearance, and regulation of nitric oxide synthase are illustrated in Figure 9. Arginine, the substrate for nitric oxide, was high-normal in JF. Any elevation of ADMA may cause a relative L-arginine deficiency resulting in lowered nitric oxide production. Thus, supplementation with arginine,

Figure 7 Follow-up hsCRP. Follow-up hsCRP demonstrated significant improvement (baseline level was 10.3).

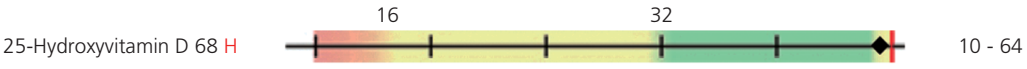

Figure 8 Follow-up vitamin D. Target level of > 55 ng/mL had been achieved.

Table 1 Reports Showing Associations of Essential Element Insufficiency with the Top Causes of Death in the United States (2005*). Conditions associated with hypertension include heart disease, cerebrovascular disease, diabetes mellitus, nephritis and nephritic syndrome, and essential hypertension.[31] NOTE: References in this table are to Lord RS, Bralley JA, eds. *Laboratory Evaluations for Integrative and Functional Medicine*. 2nd ed. Duluth, GA: Metametrix Institute; 2008:152-154.

Cause of Death*	Year of Publication: Number of Subjects						
	Calcium	Magnesium	Zinc	Selenium	Potassium	Chromium	Copper
Heart disease	2006: 110,792[36]	2006: 4,035[37] 2003: 7,172[38] 1999: 2,316[39,40] 1992: 930[41]	2006: 4,035[37] 2005: 70[42]	2005: 70[42] 1996: 3[43]	1979: 21[44]	1992: 76[45] 1991: 63[46]	2001: 80[47]
Malignant neoplasms	2007: 2,110[48] 2006: 45,306[49]	2005: 61,433[50]	2006: 857[51]	2006: 218[52,53] 1998: 974[54]			2006: 3,352[55]
Cerebrovascular diseases	2006: 110,792[36] 1999: 85,764[56]	1998: 13,922[57] 1998: 43,738[58]		2004: 1103[59]	2002: 5,600[60] 2001: 9,805[61]		1995: 149[62]
Chronic respiratory diseases		1997: 20[63]		1995: 79[64] 1983: 81[65]			
Diabetes mellitus	2006: 83,779[66]	2004: 39,345[67] 1994: 20[68] 1992: 37[69]	2004: 39,345[67] 1994: 20[68]	2005: 1,247[70] 2005: 92[71] 2005: 194[72]		2006: 36[73] 1997: 180[74]	
Alzheimer's disease		2005: 6[75]		1986: 25[76]			2005: 32[77]
Nephritis, nephritic syndrome			2005: 72[72]	1985: 78[78]			
Liver disease			1995: 253[79]	1992: 188[80]			
Essential hypertension	1991: 1,928[81] 1985: 80[82] 1982: 90[83]	2005: 12,344[12] 1999: 7,731[84] 1998: 60[85] 1992: 30,681[86]	1995: 62[87]	1998: 57[88] 1992: 3,016[89]	2001: 17,030[90]	1991: 63[46]	1995: 62[87]

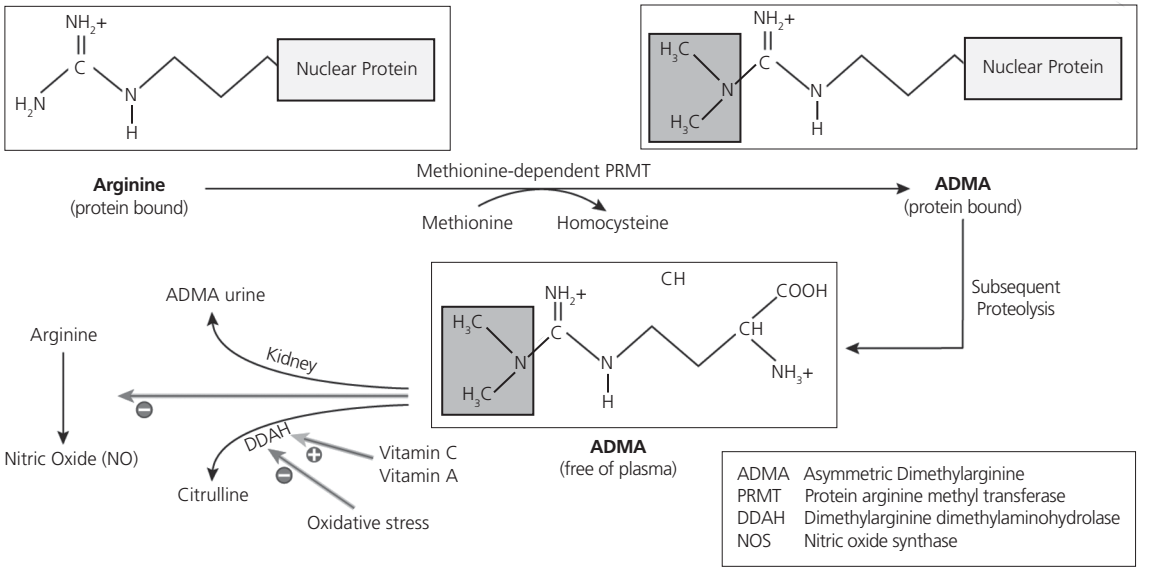

Figure 9 ADMA Synthesis, Clearance, & Regulation of NOS. Methylation of the terminal nitrogen atom of the arginine side chain in nuclear proteins produces protein-bound ADMA that is released on proteolysis. The released ADMA binds to NOS, slowing its activity in NO formation, thus regulating the rate of NO synthesis. The half-life of ADMA is governed partly by DDAH activity that causes degradation to citrulline. Because DDAH is susceptible to damage by cellular oxidants, its protection by vitamin C and vitamin A allows normal ADMA removal and, thus, normal NO formation.

even in states of apparent sufficiency, may be indicated.[22] In this case, treatment included sustained-release arginine to address both the high blood pressure and erectile dysfunction.[23]

Laboratory assessment also revealed elevated quinolinate and hs-CRP (Figure 2), both of which are associated with systemic inflammation, possibly from insulin resistance and/or an occult infection (e.g., periodontal disease).[17,24,25] Anti-inflammatory treatment approaches were used, including ascorbic acid and magnesium supplementation. JF was also put on an oral hygiene regimen using an oral irrigation system, and was instructed to avoid sugars and processed carbohydrates. Cinnamon was prescribed because of its apparent favorable effect on insulin sensitivity and its antimicrobial properties.[12]

An elevation of 8-OHdG was discovered (Figure 3). This elevation correlates with DNA oxidative damage. In association with hypertension, nitric oxide is thought to lose its beneficial physiological effects in the presence of oxygen radicals.[21] Therefore, additional vitamin C was given as an antioxidant to address oxidative stress; on follow-up testing, the hsCRP was significantly reduced (Figure 7).

Despite supplementation with magnesium, JF's RBC magnesium level was low (Figure 4). RBC magnesium concentrations significantly lower in hypertensive patients than in controls have been reported.[8] Additionally, magnesium deficiency has been associated with multiple hypertension-related causes of death (Table 1).[26,27]

Elevated triglycerides and low HDL are indicative of probable insulin resistance despite the normal fasting insulin (Figure 5). The TG/HDL ratio has a high predictive value of a first coronary event regardless of BMI.[28] The DASH diet, exercise and cinnamon were started to improve insulin sensitivity.

JF's elevated coenzyme Q10 and alpha-tocopherol levels (Figure 6) were likely from supplementation, so his vitamin E dosage was decreased. His elevated serum CoQ10 was determined to be advantageous for him. CoQ10 is nontoxic at higher levels, and is beneficial for patients with high 8-OHdG and cardiovascular risks.[13] Since vitamin E supplementation has had mixed reviews in the literature, it was considered wise to keep that level within normal limits.[14,15] Figure 6 also shows that his vitamin D level was low. Vitamin D insufficiency has been associated with hypertension, inflammation and oxidative stress.[11] Persons with chronic disease are recommended to maintain levels between 55 and 70 ng/mL, as was the goal in this case.[29] The four-month follow-up vitamin D level was 68 ng/mL (Figure 8), right in the target range.

JF initially presented with an elevated blood pressure of 162/104, despite three different antihypertensive medications. He was 30 pounds overweight, under much stress, and he consumed a poor diet. His history included a hypertensive crisis resulting in diastolic dysfunction and congestive heart failure. After four months of treatment using nutrients and diet and lifestyle intervention, his average blood pressure was 135/85. He lost 25 pounds. His medications were reduced: amlodipine and olmesartan medoxomil 20 mg/40 mg to 10 mg/20 mg and carvedilol 40 mg to 12.5 mg. At these amounts, he reported resolution or improvement in all side effects, including ED. It was anticipated that continued adherence to supplement protocol, with adjustments of dosages as needed, and an increasingly vigorous exercise program would further reduce his blood pressure over time.

CONCLUSION

Hypertension is a worldwide epidemic.[30] The morbidity, mortality and financial cost to society of untreated or undertreated hypertension are remarkably high. Despite this fact, a 2010 report from the Institute of Medicine noted that hypertension is a neglected disease. It is suggested that medication-related side effects are partly responsible.

As demonstrated in this case study, however, resistant hypertension was modified using a combination of lifestyle changes and nutrients. Using advanced laboratory analysis to identify the specific factors associated with the patient's hypertension, an effective, individualized plan was designed. The patient was able to lower the dosages of his medications to tolerable, side-effect-free levels. In so doing, he improved his health and well-being, while significantly reducing the risk of recurrence of a hypertensive crisis, congestive heart failure and other associated diseases.

Given the dire consequences of hypertension on health, investigation into the efficacy of this safe and effective individualized-plan approach to treatment is warranted.

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