Hypertension

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Dietary Nitrate Provides Sustained Blood Pressure Lowering in Hypertensive Patients

A Randomized, Phase 2, Double-Blind, Placebo-Controlled Study

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Abstract

Abstract—

Single dose administration of dietary inorganic nitrate acutely reduces blood pressure (BP) in normotensive healthy volunteers, via bioconversion to the vasodilator nitric oxide. We assessed whether dietary nitrate might provide sustained BP lowering in patients with hypertension. We randomly assigned 68 patients with hypertension in a double-blind, placebo-controlled clinical trial to receive daily dietary supplementation for 4 weeks with either dietary nitrate (250 mL daily, as beetroot juice) or a placebo (250 mL daily, as nitrate-free beetroot juice) after a 2-week run-in period and followed by a 2-week washout. We performed stratified randomization of drug-naive (n=34) and treated (n=34) patients with hypertension aged 18 to 85 years. The primary end point was change in clinic, ambulatory, and home BP compared with placebo. Daily supplementation with dietary nitrate was associated with reduction in BP measured by 3 different methods. Mean (95% confidence interval) reduction in clinic BP was 7.7/2.4 mm Hg (3.6–11.8/0.0–4.9, $P<0.001$ and $P=0.050$). Twenty-four-hour ambulatory BP was reduced by 7.7/5.2 mm Hg (4.1–11.2/2.7–7.7, $P<0.001$ for both). Home BP was reduced by 8.1/3.8 mm Hg (3.8–12.4/0.7–6.9, $P<0.001$ and $P<0.01$) with no evidence of tachyphylaxis over the 4-week intervention period. Endothelial function improved by ≈20% ($P<0.001$), and arterial stiffness was reduced by 0.59 m/s (0.24–0.93; $P<0.01$) after dietary nitrate consumption with no change after placebo. The intervention was well tolerated. This is the first evidence of durable BP reduction with dietary nitrate supplementation in a relevant patient group. These findings suggest a role for dietary nitrate as an affordable, readily-available, adjunctive treatment in the management of patients with hypertension (funded by The British Heart Foundation).

Clinical Trial Registration—

URL: http://www.clinicaltrials.gov. Unique identifier: NCT01405898.

Introduction

Systemic hypertension remains the largest attributable risk factor for mortality worldwide.[1,2] Worryingly, the scale of the problem is increasing, with the proportion of adults with hypertension predicted to increase to almost 1 in 3 (1.57 billion) by 2025.[3] Despite >60 years of innovation in the pharmacotherapy of hypertension,[4] only ≈half of hypertensives are treated for their blood pressure (BP) and of those only ≈half are controlled to guideline-driven targets.[5,6] Thus, novel therapeutic strategies including dietary approaches are of great interest.

An approach that has been explored in the treatment of hypertension is the delivery of the potent vasodilator nitric oxide (NO). Endothelial NO generation, achieved through the conventional L-arginine/NO synthase pathway, plays a critical role in sustaining vascular health. However, in most cardiovascular diseases (CVDs), including hypertension, the levels of endothelial NO are diminished.[7,8] Accordingly, therapeutic strategies restoring NO levels in hypertension have been explored. However, supplementation with substrate (L-arginine) and other essential cofactors required for healthy NO generation from NO synthase have yielded equivocal results.[9] In addition, NO donors (organic nitrates), such as nitroglycerin, have also been tested but having problems of induced endothelial dysfunction[10] and tachphylaxis[11] that have limited their clinical utility.[12]

However, NO production from the chemical reduction of inorganic nitrite (NO_2^-), a phenomenon previously thought to occur only in extreme acidosis[13–15] has emerged as a potential pathway that might be exploited as a method for delivery of NO to the blood vessel. Evidence in healthy volunteers suggests nitrite reduction occurs readily within the circulation after elevation of plasma nitrite levels, by provision of dietary or oral inorganic nitrate salts.[16,17] It is now accepted that a significant proportion of orally ingested inorganic nitrate once absorbed across the upper intestine is extracted from the blood via the salivary glands and secreted into the oral cavity where it comes into contact with symbiotic bacteria that reduce inorganic nitrate (NO_3^-) to nitrite.[18] On swallowing the saliva, the nitrite then enters the circulation,[16,17,19] where it meets mammalian nitrite reductases that convert it to NO resulting in vasodilation[20,21] and significant BP lowering.[16,17,19] Exploitation of this NO_3^--NO_2^--NO (alternative) pathway by supplementation with dietary sources of NO_3^- (eg, beetroot juice) is associated with elevations in both plasma nitrite and cyclic guanosine monophosphate (cGMP, an exquisitely sensitive marker of bioactive NO production)[22] and significant BP reductions over 24 hours in healthy volunteers and drug-naive stage 1 patients with hypertension.[17,23] We explored in this phase 2 clinical study whether a once daily dietary nitrate supplementation for 4 weeks would confer sustained BP reduction in both drug-naive and treated patients with hypertension.

Materials and Methods

Study Design

This study was a prospective single-center, double-blind, randomized, placebo-controlled trial. Eligible patients recruited were those that satisfied a range of inclusion/exclusion criteria (see online-only Data Supplement) including aged between 18 and 85 years old, an estimated glomerular filtration rate >50 mL/min, no manifest CVD, and uncontrolled BP on ambulatory BP (ABP) monitoring (day-time BP >130/85 mm Hg).[24]

Ethics approval was granted by the East London Research Ethics Committee and the trial registered on clinicaltrials.gov. Patients were recruited between July 2011 and February 2013. Patients gave written informed consent, and the study conforms to the principles of the Declaration of Helsinki.

Study Procedures

All tests were performed at the William Harvey Clinical Research Centre. Thirty-four drug-naive and 34 treated patients with hypertension were randomized to receive either 4 weeks daily supplementation with dietary nitrate (250 mL beetroot juice, James White Drinks Ltd, Ipswich, UK) or placebo (250 mL nitrate-depleted beetroot juice,[25] James White Drinks Ltd, Ipswich, UK). Patients were asked not to alter their usual diet and to keep antihypertensive medication(s) constant (in treated patients with hypertension) over the course of the study. Patients recorded once daily home BP (using a validated oscillometric BP device:705IT, Omron Corp, Tokyo, Japan) over a 2-week run-in and then had a preintervention 24-hour ABP monitor (90207, Spacelabs Healthcare Ltd, Issaquah, WA) performed. After this, patients attended in the morning after an overnight fast for clinic BP, vascular function testing, and collection of saliva, urine, and blood samples (visit: pre). Patients were then instructed to consume 1 bottle of juice at the same time in the morning daily and continue to record home BP daily during the ensuing 4 weeks. One day before the end of this period, patients returned for ABP monitoring, and then returned the following day after an overnight fast for clinic BP, vascular function testing, and collection of saliva, urine, and blood samples (visit: post). After this visit, patients continued to measure BP at home for a 2-week washout period, at the end of which they

returned for ABP monitoring, and then returned the following day after an overnight fast for clinic BP, vascular function testing, and collection of saliva, urine, and blood samples (visit: W/O; Figure S1 in the online-only Data Supplement; for full details of BP measurements, vascular function tests, and biological sample collection, see online-only Data Supplement). Transcutaneous arterial methemoglobin concentrations were determined before venepuncture in a subset of patients (placebo n=12; dietary nitrate n=7) at all visits using a validated co-oximeter (Masimo Rad-57, Masimo Inc, Irvine, CA).

Statistical Analyses

The data in the article and in the figures are presented as mean±SD or 95% confidence intervals (CIs) for comparisons between treatment allocations, unless otherwise specified. All statistical analyses were performed using Graphpad Prism software v6. For full statistical methods, including power analyses, prespecified end points, and subgroups, see online-only Data Supplement.

Results

Of the 151 patients screened for the study, 68 patients were enrolled, of whom 64 completed the study protocol and had complete data. Four patients withdrew after randomization but before the first study visit and returned no analyzable data (Figure S2). Both dietary nitrate and placebo interventions were well tolerated. No serious adverse events were reported. Common, expected findings were beeturia and fecal discoloration. All patients completed the dietary interventions for the duration of the study. The nitrate content of the active treatment juice was 25.7±5·3 mmol/L, giving ≈6·4 mmol nitrate in a 250 mL daily dose. The nitrate content of the placebo juice was 0.028±0.008 mmol/L, giving ≈0.007 mmol nitrate daily. The nitrite content was below the limits of detection in both interventions (ie, <50 nmol/L). It has been shown previously that there are no significant differences in major cationic components (ie, sodium, potassium) of the active and placebo juices.[25] Demographics and baseline screening characteristics were similar in both treatment allocation groups (Table). All patients were confirmed to have significant hypertension by ABP monitoring at trial inception.[24]

Table. Baseline Characteristics Stratified by Treatment Allocation

Treatment Allocation	Placebo	Dietary Nitrate	Significance
Demographics			
n (female)	32 (22)	32 (16)	0.14
Age, y	56.3±16.4	57.6±13.9	0.73
BMI, kg/m^2	26.5±4.0	26.8±5.0	0.74
Medications			
Hypertension drugs	1.0±1.2	1.0±1.2	0.84
Patients on (n)			
ACE-i/ARB	10	11	
β-Blocker	3	3	
CCB	14	10	
Diuretic	5	4	
α-Blocker	2	4	

Treatment Allocation	Placebo	Dietary Nitrate	Significance
Aldosterone antagonist	1	1	
Statins	3	4	
Antiplatelet drugs	0	0	
Screening ABP, mm Hg			
SBP	148.2±10.0	149.0±11.0	0.73
DBP	88.2±8.0	88.9±9.8	0.75
HR	70.6±8.3	72.9±10.7	0.32
Biochemistry			
eGFR, mL/min	79.1±16.3	85.0±16.6	0.17
Total cholesterol:HDL-C ratio	3.4±1.3	3.1±0.7	0.37

Data are presented as mean±SD. Significance shown in the last column for unpaired Student *t* test, except for analysis of sex for which Fisher exact test was performed. ABP indicates ambulatory blood pressure; ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; and SBP, systolic blood pressure.

Dietary nitrate ingestion was associated with elevations in both nitrate and nitrite concentrations in all biological compartments assessed. These levels returned to baseline after a 2-week washout period (Figure 1; Figure S3). Importantly, plasma nitrite concentrations were also elevated from baseline by ≈2.7-fold with a mean Δ0.52 μmol/L (95% CI, 0.39–0.65) after consumption of dietary nitrate with no change in the placebo limb (P<0.001; Figure 1A). The change in circulating nitrite and nitrate levels in the dietary nitrate limb was also associated with an ≈1.4-fold increase in plasma cGMP concentrations with no change in the placebo limb (P<0.001, Figure 1D). There were no changes in transcutaneous arterial methemoglobin concentrations after either intervention (Figure S3D) and no changes from baseline or between groups in glycemic, serum biochemical, or hematological indices (Table S1).

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Figure 1. Dietary nitrate consumption elevates nitrite concentration in biological compartments in patients with hypertension. The effects of 4 weeks dietary nitrate consumption (nitrate-rich juice 250 mL daily) or placebo (nitrate-depleted juice 250 mL daily) on nitrite concentrations in (**A**) plasma, (**B**) urine, (**C**) saliva, and (**D**) plasma cGMP concentrations. Data are expressed as mean±SD. Significance shown for comparisons between treatment allocations of the change between pre and post for unpaired Student *t* test; and as +++P<0.001 for Dunnett post hoc test comparison to baseline (pre) after 2-way ANOVA for changes within each treatment allocation cohort. Pre indicates first visit preintervention; post, second visit postintervention; and W/o, third visit washout.

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Figure 2. Dietary nitrate consumption reduces clinic and 24-hour ambulatory blood pressure (ABP) in patients with hypertension. The effects of 4 weeks dietary nitrate consumption (beetroot juice 250 mL daily) or placebo (nitrate-depleted beetroot juice 250 mL daily) on clinic measures of (**A**) systolic blood pressure (SBP) and (**C**) diastolic blood pressure (DBP), and (**E**) heart rate (HR); and on 24-hour ABP measures of (**B**) SBP and (**D**) DBP and (**F**) HR. Data are expressed as mean±SD. Significance shown for comparisons between treatment allocations of the change between pre and post for unpaired Student *t* test; and as ++*P*<0.01 and +++*P*<0.001 for Dunnett post hoc test comparison to baseline (pre) after 2-way ANOVA for changes within each treatment allocation cohort. Pre indicates first visit preintervention; post, second visit postintervention; and W/o third visit washout.

The 2 treatment allocation groups were well matched for baseline (preintervention) BP and heart rate measured by the methods utilized in this study (Table S2). Consumption of dietary nitrate was associated with decreases in clinic BP (Figure 2). Clinic systolic BP (SBP) and diastolic BP (DBP) decreased compared with baseline by 7.7 mm Hg (95% CI, 3.5–11.8; *P*<0.001) and 2.4 mm Hg (95% CI, 0.0–4.9; *P*=0.050), respectively; changes not evident in the placebo group (Figure 2A and 2C). Similarly, 24-hour ABP measurements exhibited a similar pattern with a mean decrease in SBP and DBP compared with baseline of 7.7 mm Hg (95% CI, 4.1–11.2, *P*<0.001) and 5.2 mm Hg (95% CI, 2.7–7.7, *P*<0.001), respectively (Figure 2B and 2D). Observation of the hourly profile of the change in 24-hour ABP after intervention revealed that consumption of dietary nitrate was associated with reduction in BP over the entire 24-hour period for both SBP and DBP (Figure S4) compared with placebo. Splitting 24-hour ABP into day-time (07:00–23:00) and night-time (23:00–07:00) periods, dietary nitrate consumption was associated with decreases in BP in both time periods (Figure S5).

Home BP was reduced within 1 week of consumption of dietary nitrate, but not placebo, for both SBP and DBP and reduced over the entire 4-week intervention period (Figure 3A and 3B). Peak decreases in BP occurred at week 6 (ie, last week of dietary nitrate intervention), with decreases in SBP compared with placebo of 8.1 mm Hg (95% CI, 3.8–12.4; *P*<0.001) and in DBP of 3.8 mm Hg (95% CI, 0.7–6.8; *P*<0.01; Figure 3A and 3B). After washout, both SBP and DBP started to return to baseline (Figure 3). There were no changes relative to baseline or compared with placebo in heart rate after dietary nitrate intervention by any method used (Figures 2E, 2F, and 3C; Figure S5E and S5F). Change in plasma nitrite from baseline in the intervention arm correlated inversely with change in SBP measured in clinic and at home, but not with ABP (Figure S6A–S6C).

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Figure 3. Dietary nitrate consumption reduces home blood pressure (BP) over entire 4-week intervention period in patients with hypertension. The effects of 4 weeks dietary nitrate consumption (beetroot juice 250 mL daily) or placebo (nitrate-depleted beetroot juice 250 mL daily) on change in weekly (**A**) systolic blood pressure (SBP) and (**B**) diastolic blood pressure (DBP) and (**C**) heart rate (HR) from baseline (week 1) measured at home. Data are expressed as mean±SD. Significance shown for comparisons between treatment allocations for 2-way ANOVA; followed by ##*P*<0.01 and ###*P*<0.001 for Bonferroni post hoc test. The vertical dotted lines at 2 and 7 weeks signify the end of the 2-week run-in and the beginning of the washout periods.

Dietary nitrate consumption was also associated with improvements in vascular function (Figure 4). Pulse wave velocity (PWV) was reduced after dietary nitrate consumption by 0.59 m/s (95% CI, 0.24–0.93; *P*<0.01) compared with baseline and 0.58 m/s (95% CI, 0.05–1.10; *P*<0.05) compared with placebo. Augmentation index was also reduced after dietary nitrate consumption by 5.2% (95% CI, 2.9–7.5; *P*<0.001) compared with baseline and 6.1%

(95% CI, 3.0–9.1; *P*<0.01) compared with placebo. Baseline brachial artery diameter and time to peak dilatation after reactive hyperemia were similar across all treatment groups and visits (Table S3). However, dietary nitrate consumption was associated with an increase in peak flow-mediated dilatation (FMD) of 1.0% (95% CI, 0.3–1.5; *P*<0.001) not evident in the placebo limb.

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Figure 4. Dietary nitrate consumption improves arterial function in patients with hypertension. The effects of 4 weeks dietary nitrate consumption (beetroot juice 250 mL daily) or placebo (nitrate-depleted beetroot juice 250 mL daily) on clinic measures of (**A**) pulse wave velocity (PWV), (**B**) augmentation index (Aix), and (**C**) % and (**D**) absolute increase in vessel diameter with flow-mediated dilatation (FMD). Data are expressed as mean±SD. Significance shown for comparisons between treatment allocations of the change between pre and post for unpaired Student *t* test; and as ++*P*<0.01 and +++*P*<0.001 for Dunnett post hoc test comparison to baseline (pre) after 2-way ANOVA for changes within each treatment allocation cohort. Pre indicates first visit preintervention; post, second visit postintervention; and W/o, third visit washout.

A priori subgroup analyses were conducted by stratification for baseline hypertension treatment status (drug-naive or treated). We recruited n=34 into each subgroup. Four patients dropped out before receiving intervention: all 4 were in the treated hypertension arm, split equally between intervention and placebo arms. There were no differences in baseline demographics, characteristics and BPs of the subgroups (Table S4), and between the placebo and dietary nitrate subgroups.

Dietary nitrate consumption produced similar rises in plasma, urine, saliva nitrite and nitrate, and plasma cGMP in both stratified limbs (Table S5). Importantly, BP was reduced compared with placebo by all methods used in both subgroups (Figures S7 and S8). PWV velocity was not altered in drug-naive patients after dietary nitrate consumption, although endothelial function trended to improvement (*P*=0.06) though this failed to reach conventional levels of statistical significance (Figure S7C and S7D). In the treated hypertensives, PWV velocity was reduced after dietary nitrate (0.82±0.87 m/s; *P*<0.01), and endothelial function was improved (change in FMD compared with placebo: 1.1%; 95% CI, 0.1–2.0; *P*=0.04; Figure S8C and S8D).

Discussion

Previously the oxidation of endogenously generated NO to nitrite, and nitrate was viewed as a 1-way, linear termination of NO activity. However, the discovery of the NO_3^--NO_2^--NO reductive pathway, dependent on the enterosalivary circuit, has led to a radical revision of our understanding of the pathways that govern endogenous NO generation and NO metabolism.[26] This novel paradigm reveals the nitrogen oxides to be in an NO cycle that can be augmented through the provision of inorganic nitrate, given either by dietary or inorganic supplementary route. By capitalizing on this cycle, herein we show that a once daily dietary nitrate intervention augments NO generation through this pathway in patients with hypertensionto lower BP. We have demonstrated that the intervention is well tolerated, safe, and is associated with robust BP reductions measured in and out of clinic.

Dietary nitrate supplementation providing ≈6 mmol nitrate daily for 4 weeks, caused substantial increases in plasma nitrate concentrations (≈5.5-fold), and is similar to the peak fold increases in previous studies with similar doses.[23] Plasma nitrite concentration was elevated by ≈2.7-fold from baseline; the reduced fold increase compared with plasma nitrate concentrations reflecting use of the enterosalivary circulation in the bioconversion of ingested nitrate to nitrite that is critically dependent on the symbiotic relationship between oral bacteria and host.[27] In this study, dietary nitrate consumption elevated both saliva nitrate and nitrite concentrations with a ratio of saliva nitrate:nitrite of ≈3. This is similar to the ratios identified in healthy volunteers after single dose nitrate supplementation,[28,29] suggesting that the enterosalivary circulation is intact and functioning normally in patients with hypertension. In these processes, dietary (or inorganic) nitrate can be thought of as a prodrug for the generation of plasma nitrite. The half-life of nitrite in the circulation after a single oral dosing has been estimated to be ≈30 minutes.[30] In contrast, nitrate has a half-life of ≈6 hours after oral dosing of inorganic nitrate.[31] The recirculation of nitrate, however, also

extends the apparent half-life of nitrate-derived nitrite, with plasma nitrite peaking at ≈3 hours after inorganic nitrate ingestion and remaining elevated for at least a further 3 hours in both healthy and hypertensive subjects.[17,19,23]

In healthy volunteers, it has been shown that at least some of the nitrite in the swallowed saliva enters the circulation where it is chemically reduced by the action of ≥1 mammalian nitrite reductases to generate vasodilator NO.[32] That this occurs in patients with hypertension also is demonstrated biochemically in this study by increases in the downstream secondary messenger cGMP, that is elevated between 3–24 hours after dietary (or inorganic) nitrate ingestion,[19,23] confirming production of bioactive NO. Peak BP reductions coincide with these peak plasma nitrite elevation and plasma cGMP elevation, at ≈3 hours following dietary (or inorganic) nitrate ingestion,[17,19,23] and in this study, the increases in plasma nitrite concentration after dietary nitrate were associated with BP reductions measured both in- and out-of-clinic, providing further evidence that nitrite reduction to NO underlies the BP-lowering effects seen with dietary nitrate consumption.

Out-of-clinic BP measurements (ie, home and ABP) are recognized to be more predictive of target organ damage and mortality in population cohort studies[33,34] and underlies the use of all 3 methods in this study. Interestingly, the magnitude of BP reduction after dietary nitrate consumption was similar across all 3 methods of measurement with clinic BP reduced by 7.7/2.4 mm Hg, 24-hour ABP by 7.7/5.2 mm Hg, and home BP by 8.1/3.8 mm Hg. Irrespective of the method of measurement, the magnitude of BP reduction is of clinical significance because it resembles the average BP reduction achieved with a single antihypertensive medication at standard dose (9.1/5.5 mm Hg).[35] Most pharmacological treatments for raised BP give larger maximal BP reductions dependent on higher baseline BP values,[35] including following acute, single inorganic, and dietary nitrate dosing in healthy and drug-naive stage 1 patients with hypertension.[17,19,23] Thus, one may postulate that the BP-lowering effects seen in these patients with mild hypertensive phenotypes may be greater in patients with more severe hypertension. However, this has not been tested in our study and is not known at this time and there is the possibility that in patients on multiple antihypertensive agents with established vascular damage from long-standing uncontrolled hypertension, the effects could be attenuated rather than amplified.

It is noteworthy that the home BP measurements over the 4 weeks demonstrate, if anything, an increasing magnitude of the effect with time with a reversal occurring only on washout. These findings are in agreement with primate studies demonstrating no tachyphylaxis to repeated and continuous systemic nitrite administration over 2 weeks,[36] confirming an absence of the development of tolerance: a characteristic that has profoundly limited the clinical utility of the organic nitrates in CVD.[37]

Dietary nitrate consumption also improved indices of vascular function including aortic PWV, augmentation index, and FMD. PWV is the gold standard measure of arterial stiffness and is recognized as a powerful predictor of cardiovascular events.[38] The exact underlying mechanism for these changes in arterial stiffness is uncertain, but preclinical studies of age-induced arterial stiffening in mice suggest that systemic nitrite therapy reduces oxidative stress and advanced glycation end products that are associated with arterial stiffening.[39] However, it is also possible that the improvement in endothelial function measured by FMD plays a role in the improved PWV. A recent report in healthy, elderly subjects supplemented with 0.1 mmol/kg inorganic nitrate (≈6–8 mmol/d) for 4 weeks demonstrated a modest increase in FMD of 0.5%, compared with no change in the placebo group.[40] We have previously demonstrated in young healthy individuals that while a single acute dose of 8 mmol of nitrate does not alter FMD (in healthy individuals the FMD response ranges from between 7% and 14%),[28] that single acute doses ranging between 6 and 24 mmol do protect against transient endothelial dysfunction induced by forearm ischemia–reperfusion injury.[17,19]

Finally, in all of the analyses, there were no significant changes in any functional parameter measured after consumption of the nitrate-free placebo intervention. This substantiates the proposal that inorganic nitrate is responsible for the beneficial effects seen with beetroot juice. The average intake of nitrate from regular food sources (predominantly vegetables) is 1.5 to 2 mmol daily,[41] and the acceptable daily intake is set by the World Health Organization at 3.7 mg/kg per day[42] (≈4.2 mmol daily for a 70 kg person) because of concerns over methemoglobinemia and carcinogenesis. In this study, no suggestion of significant methemoglobinemia was evident, and previous studies that were associated with micromolar plasma nitrite concentration have not demonstrated clinically significant methemoglobinemia.[20,43] Although there are well established links between preformed nitrosoamines and carcinogenesis,[44] recent US National Toxicology Program reports on 2-year rodent feeding studies with nitrite[45] and a comprehensive World Health Organization report summarizing epidemiological cohort

studies in humans evaluating the risk of cancer with nitrate intake have largely assuaged concerns on carcinogenesis.[42] Importantly, vegetable intake is associated with small reductions in cancer incidence, rather than increases.[46] Patients predisposed to oxalate renal stones may need to avoid certain high-nitrate vegetables that also contain oxalate, such as spinach and beetroot. Although study participants reported no adverse effects apart from expected discoloration of urine (beeturia) and feces from the purple betacyanin pigments in beetroot, we cannot be certain that prolonged intake of beetroot juice is reliably acceptable as a therapeutic source of dietary nitrate. There is batch-to-batch variation in nitrate content of vegetables and their juices and clinical studies using beetroot juice with varying concentrations delivering between ≈4 and 24 mmol. This natural variation could be controlled by use of anion exchange resin to provide fixed nitrate concentrations.[25] Our previous studies have suggested that 4 mmol is a threshold dose for BP lowering healthy volunteers, although it is not clear from our data whether this is also true for hypertensives or what dose of dietary nitrate might provide maximal BP lowering is not known.

Overall, our results presented in this study demonstrate that dietary nitrate provision to patients with hypertension provides robust BP lowering that is dependent on the conversion of nitrate to nitrite and thence NO, with no suggestion of tachyphylaxis over a 4-week period.

Perspectives

The potential importance of our findings is substantial when one considers that each 2 mm Hg increase in SBP increases mortality because of ischemic heart disease and stroke by 7% and 10%, respectively.[47] Although the time frame of the study is too short to make any supported claims to long-term BP control or to be able to extrapolate with any confidence to target organ damage reduction or CVD events, these appropriately powered data are the first to demonstrate robust, sustained BP-lowering with dietary nitrate in patients with hypertension that require BP control (rather than healthy subjects) and as such are encouraging and should spur large-scale, long-term outcome studies to explore the utility of a dietary nitrate-based therapeutics approach to hypertension and CVD risk mitigation. Moreover, dietary nitrate provides a viable option to finally exploit the NO pathway, which has been implicated at multiple steps in the genetic architecture of BP and is a therapeutic modality targeted at gene products directly implicated in raised BP.[48] With large populations of inadequately treated patients with hypertension at higher risk of CVD,[5,6] an additional strategy, based on intake of nitrate-rich vegetables, may prove to be both cost-effective, affordable, and favorable for a public health approach to hypertension.

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Disclosures

A. Ahluwalia is a director of Heartbeet Ltd. The other authors report no conflicts.

Footnotes

The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.114.04675/-/DC1.

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Novelty and Significance

What Is New?

- Once a day dietary nitrate intervention for 4 weeks provides sustained blood pressure lowering in patients with hypertension.
- This dietary intervention also results in improved function of the blood vessels.
- Prolonged dietary nitrate use is not associated with any tachyphylaxis of the beneficial effects on the cardiovascular system.
- A once a day dietary nitrate intervention results in further blood pressure lowering in patients taking 1 to 4 other blood pressure medications.

What Is Relevant?

- Dietary nitrate exerts potent and long-lasting blood pressure decrease in hypertension that is sustained with once a day dosing for 4 weeks.
- Daily dietary nitrate ingestion provides additional blood pressure lowering beyond conventional pharmacotherapy.

Summary

A once a day dietary nitrate regimen offers a strategy to lower blood pressure in hypertension either as monotherapy or in conjunction with conventional pharmacotherapy.

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