

## ORIGINAL ARTICLE



# Treating Malignant Hypertension With the Low-Sodium, Low-Protein, and Low-Fat Rice Diet

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**BACKGROUND:** The rice diet (RD), a low-sodium (<150 mg/d), low-protein (20 g/d), and low-fat (<5 g/d) diet was used to treat patients with malignant hypertension beginning in the 1940s, before any effective antihypertensive drugs were available. We retrospectively analyzed a curated cohort of RD patients with malignant hypertension to assess factors, including dietary adherence, associated with blood pressure (BP) reduction.

**METHODS:** From 17 487 RD charts, we identified 544 malignant hypertension patients (baseline systolic BP  $\geq$ 170 mmHg and with concurrent retinal hemorrhage or papilledema), excluding those with diabetes, brain tumor, or prior sympathectomy. Outcome data were censored after any 30-day break in consecutive data. Baseline features, BP changes from baseline to week 4, and diet adherence (assessed by urinary chloride, UCI) were evaluated using summary statistics, univariate, and multivariable analyses.

**RESULTS:** Most patients participated in the RD program before antihypertensive drugs were available; only 48 (8.8%) received any antihypertensive medications in the first month. The cohort (68.9% male) had a median baseline BP of 213/128 mmHg and body mass index of 23.6 kg/m<sup>2</sup>. Median time in the program before censoring was 109 days; median total time in the RD program was 333 days. BP declined significantly within the first week, reaching 179/108 mmHg at week 4. UCI dropped from 217 to 21 mg/dL by week 4. Lower UCI, higher baseline BP, and female gender, but not retinal hemorrhage or papilledema, were associated with greater systolic BP reduction.

**CONCLUSIONS:** The low-sodium, low-fat, low-protein RD effectively lowered BP in malignant hypertension patients in 4 weeks, independent of antihypertensive medications. (*Hypertension*. 2025;83:00–00. DOI: 10.1161/HYPERTENSIONAHA.125.25073.) • [Supplement Material](#).

**Key Words:** antihypertensive agents ■ blood pressure ■ diet ■ hypertension, malignant ■ papilledema

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### See Editorial by Author

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The term malignant hypertension (MH) was introduced into the English-language literature by Drs Wagener and Keith<sup>1</sup> in 1924 to describe patients with high blood pressure (BP), diffuse vascular injury, retinal hemorrhage with or without papilledema, rapid clinical decline, and a poor prognosis. In 1928, Keith et al<sup>2</sup> reported that in a cohort of 81 patients, only “5 patients lived 2 years or longer.” Before the approval of chlorothiazide by the Food

and Drug Administration in 1958,<sup>3</sup> people with MH had no proven therapeutic options.

The rice diet (RD) was devised in the early 1940s by Dr Walter Kempner<sup>4</sup> to treat patients with uncontrolled hypertension. After early reports of its success,<sup>5</sup> thousands of people from the United States and other countries came to Durham, NC, to participate in the RD program. The clinical records of those patients provide a

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## NOVELTY AND RELEVANCE

### What Is New?

Dietary intervention is important strategy for managing hypertension, yet previous research has not examined the limit of low-sodium intake reduction on blood pressure. The extremely low-sodium rice diet reduced blood pressure effectively in patients with malignant hypertension, demonstrating the concept of Food is Medicine.

The epidemic of malignant hypertension appeared to come and go, although the reasons for this are not clear.

### What Is Relevant?

Data from the Rice Diet Program suggest that lowering sodium intake to the levels substantially lower than the current recommendation can substantially reduce blood pressure, potentially benefiting hypertension management.

### Clinical/Pathophysiological Implications?

Dietary intervention is effective in managing hypertension. Very low-sodium diets are both safe and efficacious in treating malignant hypertension and can supplement the effects of antihypertensive medications. One potential mechanism by which very low-sodium diets reduce blood pressure may involve the correction of occult volume expansion, although this needs to be verified in future research.

### Nonstandard Abbreviations and Acronyms

<b>BP</b>	blood pressure
<b>DASH-Sodium</b>	Dietary Approaches to Stop Hypertension–Sodium
<b>DBP</b>	diastolic blood pressure
<b>MH</b>	malignant hypertension
<b>NPN</b>	nonprotein nitrogen
<b>RD</b>	rice diet
<b>SBP</b>	systolic blood pressure
<b>UCI</b>	urinary chloride

unique opportunity to study the impact of this restrictive diet without the confounding effect introduced by the concomitant use of modern antihypertensives.<sup>6–8</sup> Despite a drastic decrease in the prevalence of MH over the past decades, MH is not extinct and may be increasing in countries with less advanced health care resources.<sup>9,10</sup>

Since 1950, nearly 200 randomized trials have examined the biological impact of low-sodium diets. To the best of our knowledge, and despite there being no established lower limit to the BP-lowering effects of sodium restriction,<sup>11</sup> none have evaluated a diet as restricted in sodium as the RD. Furthermore, each of these studies has had to calibrate its equipose to accommodate the use of antihypertensive medications, thereby obscuring the effects of diet per se on patients with MH.<sup>11,12</sup> In addition, although case series have reported outcomes of RD program participants,<sup>6</sup> no publication has described the impact of the RD on the full cohort of enrolled patients with MH.

We digitized the treatment records of 17 487 RD program participants, and from these records, have

constructed a database capturing key patient-level data elements.<sup>13</sup> Here, we present a retrospective interventional cohort study examining the BP response of all RD program participants with MH, the relationship between estimated sodium intake and BP responses of the participants, and patient factors that predict BP lowering.

## METHODS

The data that support the findings of this study are available in the Duke Research Data Repository at <https://research.repository.duke.edu/>.

### Study Design

The database was derived from patient-level treatment records maintained by Dr Kempner and the clinical staff of the RD program. This study focuses on patients with MH enrolled in the RD program regarding (1) weekly systolic BP (SBP) and diastolic BP (DBP) trends over 4 weeks after diet initiation; (2) the relationship between SBP and sodium intake (using urinary chloride [UCI] as a marker of sodium intake, because of the inability to measure urine sodium directly) over the first 4 weeks of RD treatment; (3) the association between patient-level factors and BP changes from entry to week 4, and (4) the above associations by MH classes (see Data analysis). BP was measured with mercury or aneroid sphygmomanometers, and UCI was analyzed in aliquots of 24-hour urine collections using the method of Volhard.<sup>14</sup> Construction of this database and the execution of this study were approved by the Duke University Medical Center Institutional Review Board (Pro00105257).

### Study Intervention

The RD was conceived by Kempner<sup>4</sup> based on his studies of *in vitro* renal cellular metabolism. This restricted diet contained <5 g/d of fat, ≈20 gm/d of protein, <150 mg/d of sodium, and <200 mg/d of chloride. Nominal daily energy intake of ≈2000

Kcal was tailored to meet individual patient weight targets. Fluid intake was limited to 0.7 to 1 L/d of fruit and fruit juices to avoid water intoxication from the low solute content of the diet. The diet was supplemented with iron, vitamins A and D, thiamine, riboflavin, and niacinamide. The RD comprised  $\approx$ 250 to 350 g of dry rice daily, boiled or steamed in water or fruit juice. All fruit juices and fruits except tomato and vegetable juices, nuts, dates, avocados, and canned or dried fruit or fruit derivatives containing anything other than white sugar or dextrose were allowed. Patients' clinical status and various biochemical variables were monitored closely during initiation of the diet, often while in the hospital. If response to the diet proved to be adequate and durable (over months), small amounts of nonleguminous vegetables, potatoes, lean meat, or fish were sometimes added.<sup>7</sup>

## Study Population

All adult patients (age  $\geq$ 18 years old) enrolled in the RD program were considered for this report. As Kempner<sup>15</sup> specified, "blood pressure readings were taken at about the same time each day by the same examiner, with the patient in a recumbent position and after a period of about 20 minute's rest." Those with at least 1 SBP  $\geq$ 170 mmHg between day  $-7$  and day 6 of the RD start date, and the presence of retinal hemorrhage or papilledema on fundoscopic examination between day  $-30$  and day 30 of starting the RD were considered for analysis. Photographic retinal images were obtained and analyzed by a dedicated ophthalmologist. Patient data were censored if there was a data entry gap of  $>$ 30 days, and only data collected before the 30-day gap were analyzed. Each patient was considered only once, and only the first visit to the RD program was analyzed for patients who returned after a 30-day break. To minimize misclassification and confounding, we excluded patients with hyperglycemia (to avoid including diabetic retinopathy), brain tumor, or previous sympathectomy.

## Statistical Analysis

Median (and interquartile range) for continuous variables, and frequency (percentage) for categorical variables were used to describe the cohort demographics. Patients with MH were further classified as described by Keith et al<sup>16</sup> having class III hypertension (with retinal hemorrhage only), class IV (with both retinal hemorrhage and papilledema), or what we have designated class V (papilledema without hemorrhage), a category of MH not described by Keith et al<sup>16</sup> that was described by Lip et al<sup>17</sup>. We kept those patients separate because we did not want to lump them arbitrarily with class IV.

Baseline SBP, DBP, urine concentration of chloride (UCI), and blood concentration of nonprotein nitrogen (NPN; laboratory reference range 25–35 mg/dL) were defined as the average of available data recorded between day  $-7$  and day  $+1$ . Baseline weight is the average of weights from day  $-2$  to day  $+1$ . The trends of SBP and DBP from baseline to week 4 are graphically shown as the weekly average (eg, week 1 BP is the average of BPs recorded between day 1 and day 7) with 95% CIs. Median (interquartile range) of SBP, DBP, and UCI were also computed for each weekly time point from baseline to Week 4.

We further defined adherence to RD by the number of weeks each participant met the goal of UCI  $\leq$ 42 mg/dL, an

optimal cut point determined from UCI changes and associated SBP responses during the first 4 weeks. Participants were classified into 3 adherence groups: high adherence (UCI goal was met for at least 3 of the 4 weeks), moderate adherence (goal was met for 1 or 2 weeks), and low adherence (goal was never achieved during the 4 weeks). Dietary adherence was also calculated as the percent of available UCI values  $\leq$ 42 mg/dL for patients with at least 6 UCI values available between week 1 and week 4. Univariable linear mixed model was used to regress weekly SBP changes from the baseline on their corresponding time of measurement (ie, week) with random intercept by patient to assess the rate of SBP change for each adherence group.

Univariable linear regression was used to evaluate the relationship between baseline characteristics (age, gender, retinal hemorrhage, papilledema, SBP, NPN, UCI, dietary adherence, and weight) and SBP changes from baseline to week 4 (or week 3 if no week 4 data were available). Baseline characteristics with a  $P < 0.15$  in the univariable analysis were selected for multivariable linear regression modeling, including baseline SBP as a covariate. Variables meeting  $P < 0.05$  were considered significant. To evaluate any possible influence of BP medications, sensitivity testing was conducted in patients who were not taking BP medications during the first 4 weeks.

Lastly, we defined responders to the RD as those who achieved  $>$ 5% BP reduction from baseline to week 4 and compared their characteristics to those of nonresponders ( $\leq$ 5% BP reduction).

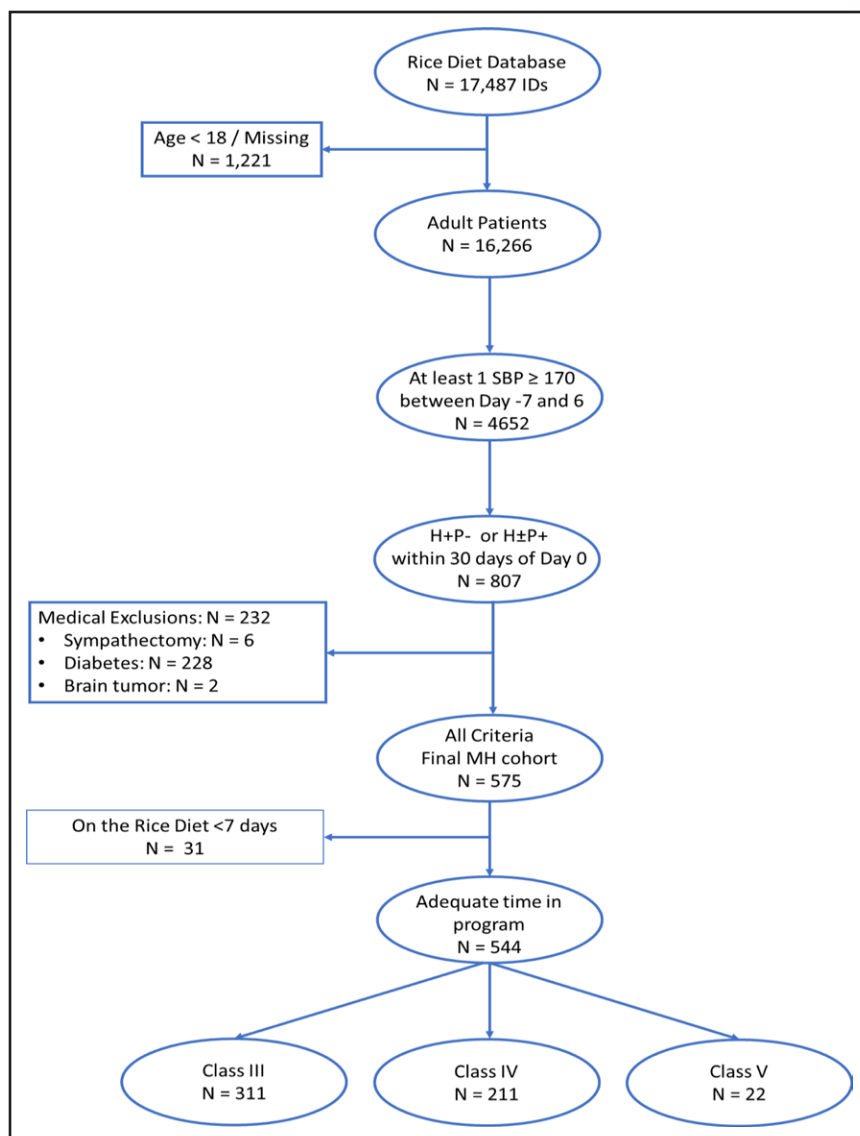
## RESULTS

### Demographics and Baseline Values

The RD program database contains data from 16266 adults (Figure 1). Of the 807 patients with SBP  $\geq$ 170 mmHg between day  $-7$  and  $+6$  and with concomitant retinal hemorrhage, papilledema, or both, 232 were excluded because of 1 or more of the following: overt diabetes or hyperglycemia ( $n=228$ ), prior sympathectomy ( $n=6$ ), brain tumor ( $n=2$ ); another 31 were excluded because they participated in the RD program for  $<$ 7 days. The final cohort of 544 analyzable patients with MH includes 311 with retinal hemorrhage (Keith et al<sup>16</sup> class III), 211 with hemorrhage and papilledema (Keith et al<sup>16</sup> class IV), and 22 with papilledema only (class V).

Figure 2 shows the number of patients with MH who attended the RD program for the first time per 3-year interval. Few participated during 1940 to 1942, but the number increased thereafter, peaking during 1949 to 1951. Subsequently, patient arrivals dropped drastically until around 1955, after which the rate of accrual dropped slowly but did not entirely disappear.

Demographic and clinical characteristics for the cohort are displayed in Table 1. Patients were predominantly male (68.9%); median age was 50 (range, 19–81), and  $>$ 90% of the cohort was enrolled before effective antihypertensive medication was introduced in 1958. The median (interquartile range) for key variables is as follows: days spent in the program before a 30-day



**Figure 1. Patient flowchart.** MH indicates malignant hypertension; and SBP, systolic blood pressure.

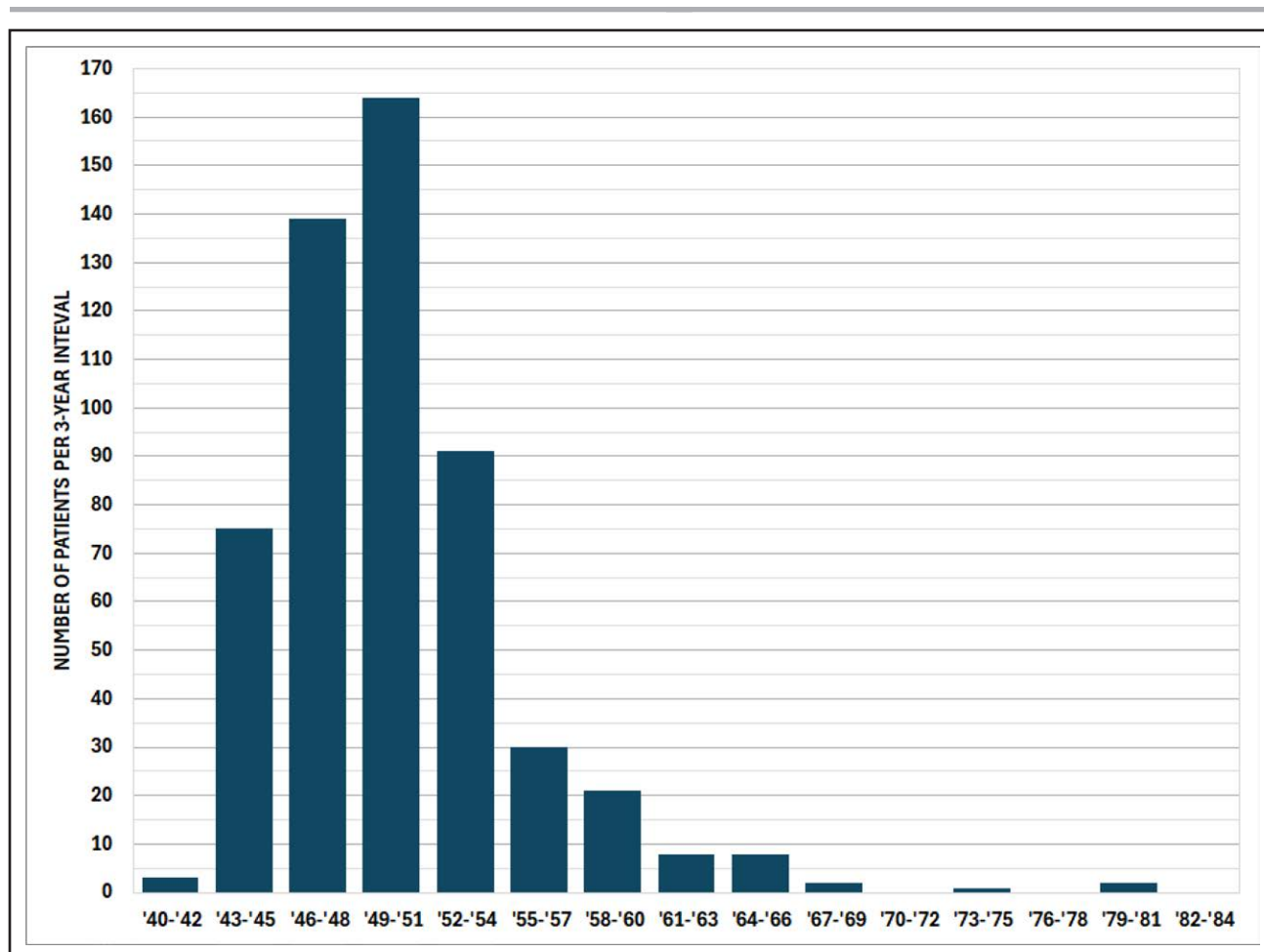
or longer data break was 109 days (46.0–176); baseline SBP was 213 mmHg (194–232) and DBP was 128 mmHg (114–140); baseline weight was 69.2 kg (60.2–78.1) and body mass index was 23.6 (21.5–27.3) kg/m<sup>2</sup> (unfortunately, a large number of patients had no recorded weight [61.8%] or height [23.5%] data); and baseline NPN was 41.0 mg/dL (35–57) and 24-hour UCI was 217 mg/dL (113–356). Presuming patients were at steady state and making ≈1 L of urine per day, this UCI is consistent with a sodium intake of ≈1430 mg per day at study entry. We think that this value may be low due to sodium restriction in some patients before starting the RD.

Only 48 (8.8%) of the 544 patients received antihypertensive drugs for even 1 day during their first 4 weeks on the RD; 38 were treated with a single agent, 6 with 2, and 4 with 3 agents. Medications used and number of patients taking each were rauwolfia (22), hydralazine (12), papaverine (10), thiazides (7), guanethedine (2),

pentolinium (2), mercurial diuretics (2), hexamethonium (1), spironolactone (1), ethacrynic acid (1), veratrum (1), and nadolol (1). About half of the 48 patients had antihypertensive drugs discontinued during the first 4 weeks. During the first 4 weeks on the RD, 23 patients (4.2%) died.

### BP Response and Relationship With Chloride Excretion

SBP and DBP fell continuously from entry to week 4 (Figure 3A). When the BP changes for each MH class were examined separately, BP reduction relative to baseline was consistent and similar across the 3 classes and was already apparent by week 1 (Figure 3B). In addition to BP, UCI declined continuously from baseline to week 4 across the MH classes, and the trend appears to track with the reduction of SBP/DBP (Figure 3C). The median weight for the cohort dropped 2.1 kg between



**Figure 2.** Number of participants first attending the Rice Diet Program per 3-year interval.

baseline and week 4, but notably, >50% of patients were missing a recorded weight at week 1, and >60% were missing a recorded weight during week 4.

Figure 4 shows further examination of the relationship between percent changes in SBP over 4 weeks for each RD adherence group. Those judged to have high diet adherence (ie, UCI at goal for 3 or 4 weeks) had the greatest reduction in SBP, up to an average of 5.32% reduction for each additional week in the program ( $\beta$ ,  $-5.06$  [95% CI,  $-5.32$  to  $-4.8$ ] for time variable). The SBP reduction was significant over time and similar between the moderate and low adherence groups ( $\beta$ ,  $-3.79$  versus  $-3.27$ ), but the level of reduction was smaller than that in the high adherence group ( $\beta$ ,  $-5.06$ ).

### Predictors of BP Response

The relationship between baseline characteristics (age, gender, MH classification, SBP, DBP, NPN, UCI, and weight), dietary adherence (indicated by the percent of time UCI was  $\leq 42$  mg/dL, a value corresponding to a 24-hour urinary sodium excretion of  $\approx 250$  mg/d), and SBP and DBP changes from baseline to week 4 were

examined using univariable and multivariable regression analyses (Table 2). Univariable analysis (Table 2) revealed that female gender, class IV (versus III), but not class V, higher entry SBP, lower entry NPN, higher baseline UCI, and a greater dietary adherence were all associated with a greater reduction in SBP at week 4. Only baseline DBP, UCI, and dietary adherence were significantly associated with DBP changes at week 4. Class V versus class IV was not significantly associated with changes in either SBP or DBP.

The multivariable linear regression analysis identified multiple significant predictors for SBP and DBP changes at 4 weeks (Table 2). Women had a greater SBP reduction at week 4. In addition, higher baseline BP (either SBP or DBP) and greater dietary adherence were significantly associated with greater reductions in SBP and DBP; baseline NPN was no longer significant, suggesting that, when accounting for all variables together, baseline renal function did not significantly impact SBP reduction from sodium restriction. Based on the multivariable analysis, an increase in dietary adherence by 10 percentage points over 4 weeks was associated with an estimated reduction of 3.1 mmHg in SBP and 1.2



**Table 1. Rice Diet Malignant Hypertension Cohort Baseline Characteristics**

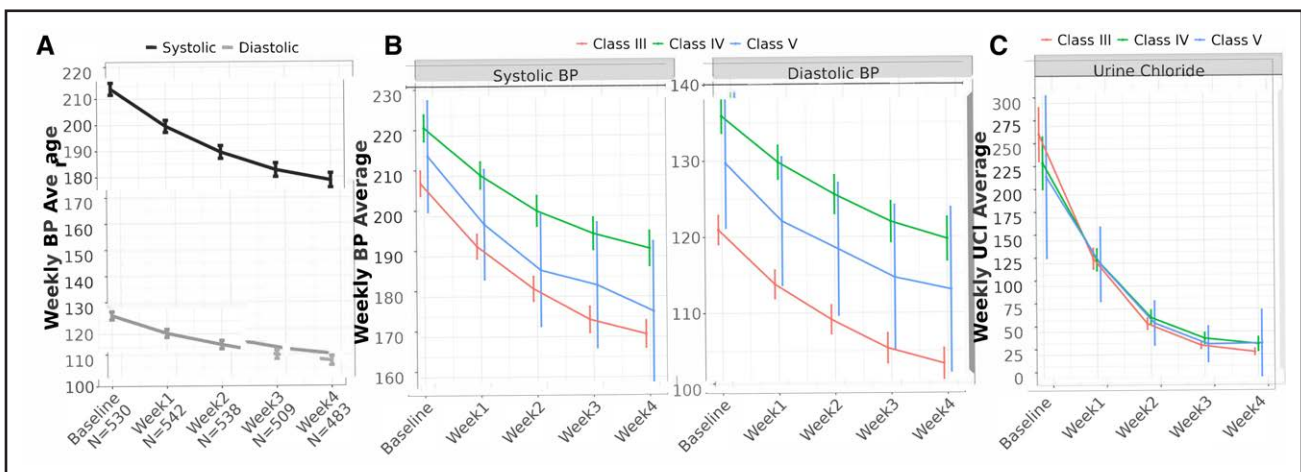
	Class III (H+P-); n=311	Class IV (H+P+); n=211	Class V (H-P+); n=22	Total; N=544
Age, y	53.0 [47.0, 59.0]	46.0 [39.5, 53.5]	41.5 [37.0, 49.0]	50.0 [42.0, 57.0]
Male	199 (64.0%)	162 (76.8%)	14 (63.6%)	375 (68.9%)
Program start before 1958	284 (91.3%)	197 (93.4%)	21 (95.5%)	502 (92.3%)
Time in program, before 30-d break	117 [53.5, 180]	89.0 [37.0, 168]	110 [48.3, 178]	109 [46.0, 176]
Time in program, total, d	440 [148, 1530]	180 [52.5, 697]	552 [162, 1580]	333 [89.0, 1110]
SBP, mmHg	207 [189, 223]	223 [210, 238]	211 [196, 244]	213 [194, 232]
Nmiss	9 (2.9%)	3 (1.4%)	2 (9.1%)	14 (2.6%)
DBP, mmHg	120 [109, 134]	137 [127, 146]	133 [120, 141]	128 [114, 140]
Nmiss	9 (2.9%)	3 (1.4%)	2 (9.1%)	14 (2.6%)
Weight, kg	69.1 [61.1, 77.9]	68.9 [59.8, 77.0]	76.3 [65.5, 83.3]	69.2 [60.2, 78.1]
Nmiss	197 (63.3%)	123 (58.3%)	16 (72.7%)	336 (61.8%)
BMI, kg/m <sup>2</sup>	23.9 [22.0, 27.7]	23.5 [21.4, 26.2]	25.5 [22.0, 29.4]	23.6 [21.5, 27.3]
Nmiss	215 (69.1%)	140 (66.4%)	16 (72.7%)	371 (68.2%)
UCI, mg/dL	242 [117, 365]	194 [108, 341]	215 [102, 268]	217 [113, 356]
Nmiss	155 (49.8%)	99 (46.9%)	9 (40.9%)	263 (48.3%)
NPN, mg/dL	38.0 [33.5, 45.0]	51.0 [39.0, 72.0]	44.5 [37.0, 51.0]	41.0 [35.0, 57.0]
Nmiss	132 (42.4%)	74 (35.1%)	11 (50.0%)	217 (39.9%)
BP medication during first 4 wk, n (%)	23 (7.4%)	24 (11.4%)	1 (4.5%)	48 (8.8%)
Death during first 4 wk, n (%)	6 (1.9%)	17 (8.1%)	0 (0%)	23 (4.2%)

Values are median [Q1, Q3] or n (%). SBP, DBP, NPN, UCI entry: average from day -7 to day 1. Weight entry: average from day -2 to day 1. BMI indicates body mass index; BP, blood pressure; DBP, diastolic blood pressure; NPN, nonprotein nitrogen; SBP, systolic blood pressure; and UCI, urinary chloride.

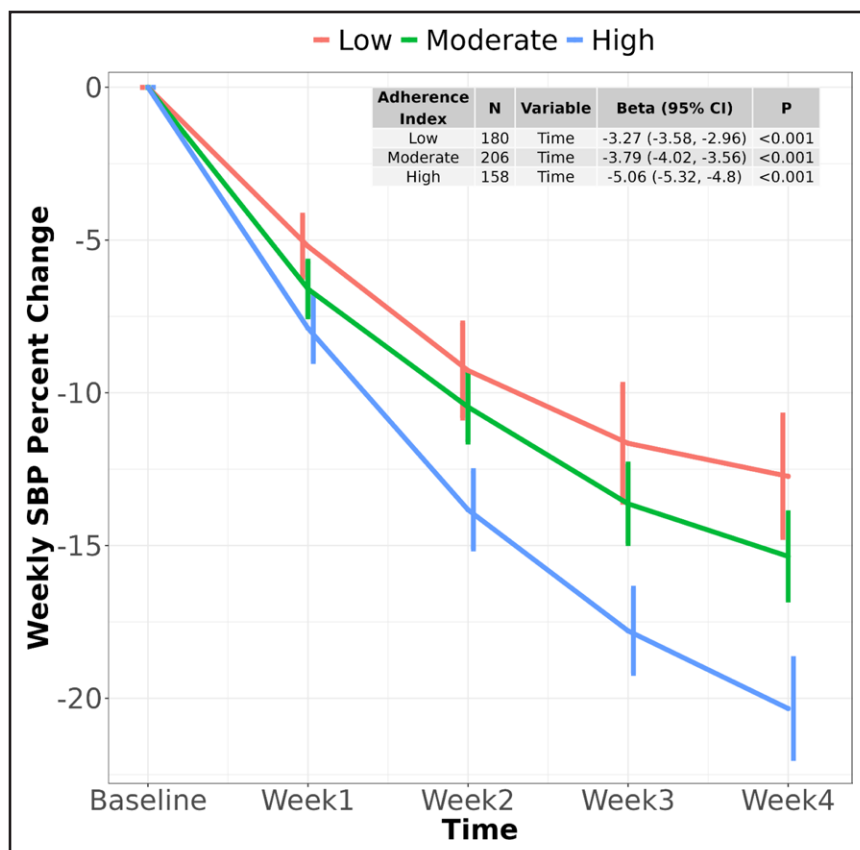
mmHg in DBP. Furthermore, linear regression analysis revealed that a reduction in weekly UCI levels significantly predicted lower SBP during weeks 2 through 4, with the strength of this association increasing over 4 weeks (Table S1).

Among the 477 patients with BP data at both baseline and week 4, the majority (85.3%, n=407) were considered responders (>5% BP reduction at week 4). The responders and nonresponders were similar in age, baseline BP, weight, and NPN, but nonresponders had a higher proportion of males and a lower baseline UCI. Among

the responders, 86.8% reached goal of UCI at week 4, whereas the comparable figure for nonresponders was 55.8%. The SBP of the 70 out of 475 (14.7%) who were considered nonresponders either increased or fell by <5%. Only about 16% of nonresponders had high dietary adherence as indicated by UCI at goal for 3 or 4 weeks; nearly half (47%) had low adherence, and 37% had moderate adherence. Sensitivity analysis on the data sets that excluded the 48 patients who were on BP medications by multivariable linear regression still led to consistent results as the main analysis (Table S2).

**Figure 3. xxx.**

Weekly blood pressure of the participants (BP) from baseline to week 4 for the entire cohort (A), by malignant hypertension (MH) classes (B), and the weekly urinary chloride (UCI) by MH classes (C).



**Figure 4. Weekly systolic blood pressure (SBP) changes grouped by urinary chloride (UCI) indexed adherence.**

The effect of baseline SBP and time on weekly SBP change is listed by regression coefficient,  $\beta$ , and its 95% CI. UCI adherence is assigned as high when meeting UCI goal of  $\leq 42$  mg/dL for 3 or 4 weeks during the first 4 weeks; moderate if at goal for 1 to 2 weeks; or low if none of the 4 weeks at goal.

## DISCUSSION

The RD offered people with MH a chance for improved BP control at a time when there were no effective, Food and Drug Administration–approved antihypertensive medications. This study describes the changes in BP for a large cohort of patients with MH, as well as patient-level factors predicting a BP response to the RD. The retrospective nature of this investigation and the concurrent nonsodium dietary restrictions (ie, fat and protein) limit precise conclusions, but the data do offer a rare opportunity to examine BP changes at levels of sodium intake well below current dietary recommendations of 1500 mg/d.<sup>18</sup>

The BP reductions found in this study were arguably the most striking finding. By week 4, the median SBP and DBP had fallen by 35.1 and 16.6 mmHg, respectively. Although no modern studies compare directly with this cohort, in 1950, Watkins<sup>19</sup> published findings from a group of 50 severely hypertensive inpatients in New York who were placed on the RD. They noted SBP/DBP changes of  $-29/-16$  mmHg over 3 weeks, similar to the results seen in the present study, although they did note that BP in their cohort fell by  $-9/-3$  mmHg during a 3-week control phase before the initiation of the RD, suggesting that early BP changes may not be entirely attributable to the dietary intervention. In the study of Watkins,<sup>19</sup> 8% of patients

had either unchanged or a higher BP after 3 weeks on the RD. In the present study, 70 patients (14.7%) had  $<5\%$  BP reduction at week 4, despite more than half of them (52.9%) adhering to the RD as indicated by UCI.

An interesting question raised by the RD data is whether the BP-lowering effects are attributable to sodium restriction alone. Kempner was satisfied with the results of the diet and never investigated this aspect. However, Watkins<sup>19</sup> noted that adding 1 to 3 g of sodium chloride to the RD reversed BP improvements in several individuals, while neither protein nor fat supplementation had an effect. Furthermore, a meticulous study by Dole et al<sup>20</sup> of 6 patients with hypertension hospitalized for 6 months on a metabolic ward and fed the RD, showed the average SBP fell from 202.7 to 161.5, which largely reversed with the addition of sodium chloride but not ammonium chloride, prompting their conclusion: "Restriction of sodium, but not of chloride appeared to be necessary for the clinical effect." Finally, a tightly controlled study of 8 patients with hypertension by Chapman et al<sup>21</sup> published in 1950, demonstrated a dramatic decline in BP on what they called the "Rice-Fruit" diet (based on Dr Kempner's), with normalization of BP in 2 patients and a more than 25 mmHg decline of SBP in 5 patients. They noted that the BP-lowering effects of this diet were not mitigated by protein supplementation (40 g) but were largely reversed by the addition of sodium (10

**Table 2. Univariable and Multivariable Linear Regressions Examining the Change in SBP Between Baseline and Week 4**

Univariable linear regression:					
	N	SBP change		DBP change	
		$\beta$ (95% CI)	P value	$\beta$ (95% CI)	P value
Age, y	501	-0.13 (-0.34 to 0.08)	0.217	0.03 (-0.08 to 0.15)	0.602
Male (vs female)	501	11.57 (7.04 to 16.1)	<0.001	1.91 (-0.66 to 4.47)	0.145
Hypertension class					
Class IV (vs III)	501	7.20 (2.79 to 11.62)	0.001	1.50 (-0.97 to 3.96)	0.233
Class V (vs III)	501	-0.68 (-12.2 to 10.9)	0.908	0.93 (-5.51 to 7.38)	0.776
Baseline SBP or DBP, mm Hg	501	-0.25 (-0.33 to -0.17)	<0.001	-0.17 (-0.24 to -0.11)	<0.001
Baseline NPN, mg/dL	305	0.18 (0.08 to 0.27)	<0.001	0.03 (-0.02 to 0.09)	0.243
Baseline UCl, mg/dL	269	-0.02 (-0.04 to -0.01)	0.004	-0.01 (-0.02 to 0)	0.032
UCl compliance %	360	-0.31 (-0.39 to -0.22)	<0.001	-0.12 (-0.17 to -0.08)	<0.001
Baseline weight, kg	192	-0.05 (-0.26 to 0.16)	0.646	-0.07 (-0.19 to 0.05)	0.235
Multivariable linear regression:					
		$\beta$ (95% CI)	P value		
SBP change multivariable linear model (n=228)					
Baseline SBP, mm Hg		-0.30 (-0.41 to -0.19)	<0.001		
Male (vs female)		6.59 (0.03 to 13.15)	0.049		
Hypertension class					
Class IV (vs III)		6.23 (-0.24 to 12.71)	0.059		
Class V (vs III)		0.04 (-15.7 to 15.7)	0.996		
Baseline NPN, mg/dL		-0.03 (-0.14 to 0.08)	0.574		
UCl compliance %		-0.34 (-0.46 to -0.23)	<0.001		
DBP change multivariable linear model (n=360)					
Baseline DBP, mm Hg		-0.22 (-0.29 to -0.15)	<0.001		
Male (vs female)		1.91 (-0.89 to 4.71)	0.182		
UCl compliance %		-0.12 (-0.17 to -0.08)	<0.001		

DBP indicates diastolic blood pressure; NPN, nonprotein nitrogen; SBP, systolic blood pressure; and UCl, urinary chloride.

\*Total sample size for the analysis data set.

g). Concurrent evaluation of body composition in these subjects revealed significant weight loss (1.47 kg/wk over an average of  $\approx$ 4 weeks), mostly attributed to loss of extracellular fluid and fat. However, the authors also highlighted some loss of “active tissue” (“presumably mostly muscle”), raising concerns about the safety and necessity of such severe protein restriction.<sup>21</sup> By comparison, the DASH-Sodium trial (Dietary Approaches to Stop Hypertension–Sodium), which evaluated 3 levels of dietary sodium intake (1.15, 2.3, and 3.45 g/d) using both DASH and control diets, found that lower sodium intake led to a linear reduction in BP in both diet groups.<sup>22</sup> The greatest decrease in BP occurred when the DASH diet was combined with the lowest sodium intake, although sodium restriction produced relatively less BP lowering in the DASH cohort, perhaps because the BP was already lower in the DASH than the control diet group. Taken in total, these observations raise questions about the value of fat and protein restriction in the RD.

We also found an inverse, linear relationship between sodium intake (UCl) and BP, even at levels of UCl  $\leq$ 42

mg/dL (ie, estimated sodium intake  $\leq$ 250 mg/d), which is 6 times lower than current dietary recommendations for sodium intake ( $<$ 1.5 g/d) for patients with hypertension. A rigorous meta-analysis by Fillippini et al, who examined the dose response of BP to sodium restriction in randomized trials that measured 24-hour sodium excretion (sodium range, 0.4–7.6 g/d), provides further evidence; they also found an inverse linear relationship between BP and sodium intake, although they did not evaluate sodium intakes as low as those of the RD.<sup>11</sup> These observations imply that sodium targets even lower than current guidelines, not necessarily to the extremely low level used in RD, might offer a potent nonpharmacological strategy for reducing BP and mitigating vascular injury.

Notably, although there are similarities between our findings and modern trials, it is difficult to directly compare results or to confidently conclude that differences in clinical outcomes are solely attributable to differences in sodium intake. For example, the RD MH cohort had entry BP well above that in contemporary studies, possibly



limiting participants' relative diet sensitivity (as our multivariate analysis suggests), whereas contemporary studies may limit their absolute potential BP response by starting with BP closer to the target range. In a subanalysis of the DASH-Sodium trial noted above, participants on the low-sodium DASH diet (1150 mg/d) with a baseline BP >150 mm Hg had their SBP reduced by 20.8 mm Hg after 4 weeks, versus 35.5 mm Hg seen here.<sup>23</sup> However, the mean baseline SBP in the hypertensive subcohort of the DASH-Sodium trial was 154.4 mm Hg versus 213 mm Hg in the RD MH cohort.

Multivariate analysis of the baseline characteristics of our cohort shows that female gender and a higher baseline BP best predict BP lowering on the RD. It also shows that people with class III retinopathy (hemorrhage without papilledema) had a better BP-lowering response to the RD than did those with class IV retinopathy (hemorrhage with papilledema). Possibly class IV retinopathy reflects more advanced vascular disease or less salt sensitivity. It is interesting that higher NPN, a predecessor to blood urea nitrogen and a no-longer-used marker of renal function,<sup>24</sup> was inversely related to BP lowering on univariate analysis, but not on multivariate analysis, which controls for retinopathy class. Given the fallibility of NPN as a measure of renal function, it is difficult to draw firm conclusions from this association.

An unexpected observation from the present study regards the accrual rate of patients over the course of 40 years (1942–1982). As shown in Figure 2, the number of patients coming to the RD increased rapidly as the existence of the program became known. However, after a peak in about 1950, there was a precipitous (near-exponential) drop in accruals until about 1958. Others have noted the “disappearance” of MH,<sup>25</sup> and most<sup>26</sup> assume or imply that the decreased prevalence results from the availability of effective antihypertensive medication. As is the case for some other diseases that have dramatically declined in prevalence, such as coronary heart disease<sup>27,28</sup> or rheumatic fever,<sup>29</sup> our data suggest that something other than pharmacotherapy is at play because the decline in patient accrual began years before effective antihypertensive medications were available. Although unlikely, we cannot rule out the possibility of a decline in patient referrals to the RD by primary care physicians.

With the current widespread availability of antihypertensive medications and the relentless marketing of inexpensive processed foods, it is practical to consider the willingness of the patients to endure a diet that Dr Kempner reportedly described as “monotonous and tasteless” and predicted “would never become popular.”<sup>8</sup> By contrast, at the inception of the RD, the stakes were different. Patients with MH came to the program with a dire prognosis and few options, which likely motivated them to adhere to the dietary treatment as their primary source of hope. Additionally, support from other patients

in the same program facing similar prognoses may also have contributed to the high adherence indicated by the UCI data. Anecdotally, noted physician, Paul Dudley White,<sup>30</sup> visited the program in person, sampled a meal, and reported that it was “quite palatable.” Unfortunately, it is unclear from available records whether the nature of RD and the increased availability of antihypertensives contributed to patient dropout or to the decline in patient referrals after 1958.

Finally, it is important to note that RD had contemporary critics who voiced safety concerns about its low-protein and salt content. It was argued by some that the protein content was insufficient to avoid catabolism of lean muscle and vital organs. In his 1948 publication, Dr Kempner<sup>4</sup> refuted this charge, explaining that the protein-sparing effect of carbohydrates helps maintain protein equilibrium and pointing to stable hemoglobin and reduced blood urea nitrogen and NPN levels to support this. This is somewhat at odds with the metabolic studies cited above, where some patients appeared to lose muscle mass on the diet.<sup>21</sup> An additional concern was the risk of abnormal serum sodium concentrations, particularly in those with renal disease and salt wasting who were noted to have a high mortality rate.<sup>6</sup> In recognition of these risks, Kempner<sup>4</sup> recommended that patients “should be under constant medical supervision and blood and urine chemistry should be checked frequently” in the earliest phases of RD.

Although rigorous methodologies were used to create and archive data from the RD program, and to conduct this analysis, there are important limitations. First, because of its retrospective nature, it is impossible to control for potential confounders. For example, this study used only observations made as part of patient care, rather than a standardized research protocol, so the timing and collection of clinical and metabolic variables were incomplete and nonuniform, which reduces statistical power and may result in measurement bias. Furthermore, it is impossible to discern from the available records which data were collected on inpatients versus ambulatory patients, or exactly what, if any, modifications were made to the RD throughout each patient's clinical course. This is relevant as patients were commonly hospitalized during the initiation of the diet for close clinical monitoring. Notably, in the ambulatory setting while in the RD program at Duke, patients typically stayed in a rice house with the flexibility to come and go freely. The paucity of patient weight data prevented examination of the possible effect of loss of extracellular fluid during salt restriction on BP. Current data also do not permit distinction of the individual effects of the low sodium, low protein, and low fat on BP. Finally, although UCI is highly correlated with sodium intake, the use of UCI concentrations does not fully describe the relationship between sodium restriction and BP lowering.<sup>31</sup>

In conclusion, the RD offered patients with the dismal prognosis conferred by MH and no other viable therapeutic options an opportunity to lower their BP through a rigorous, albeit monotonous, dietary intervention requiring close medical supervision. The RD did effect a rapid reduction in BP, but because the RD restricted sodium, protein, and fat together, it is impossible to conclude with these data that its BP-lowering effects are due solely to sodium restriction. Nonetheless, these historical data suggest that patients with high BP may benefit from sodium restriction many times lower than current guidelines, particularly those whose BP elevation resists available pharmacological therapies.

## PERSPECTIVES

Before truly effective antihypertensive medications became available in the 1960s, the prognosis for patients with MH, a severe hypertension with organ damage, was poor. The RD, developed in the 1940s, was a strict yet effective dietary intervention—very low in intakes of sodium, protein, and fat. The retrospective analysis of a cohort of 544 patients with MH treated with the RD underscores the impact of the dietary intervention.

The great majority of patients in this cohort received no antihypertensive drugs during the first month of receiving the RD intervention. During this period, the median SBP declined by over 30 mmHg, accompanied by a steep drop in UCI levels, confirming dietary adherence. These changes occurred in patients with severe high baseline BP and retinal damage, highlighting the ability of diet alone to modify even the severest forms of hypertension.

Notably, greater BP reductions were associated with female gender, higher baseline BP, and lower levels of UCI, suggesting that patient-level biological factors and adherence to sodium restriction, rather than existing end-organ damage, were involved in BP response.

Despite the contemporary availability of effective antihypertensive medications today, this historical cohort points out that dietary therapy—when applied intensively and with high adherence—can achieve rapid and clinically meaningful outcomes, even in the most severe forms of hypertension. The findings from these patients with MH affirm the principle that “food is medicine,” highlighting its importance in managing hypertension.

## ARTICLE INFORMATION

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None.

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