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Environmental Determinants of Urinary Kallikrein Excretion

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Decreased urinary kallikrein excretion has been shown to be related to hypertension. Kallikrein levels also have been shown to be determined primarily by genes, with 51% of the total variance being due to a single gene. However, there exists strong spouse-spouse correlation, indicating that common environment plays a significant role. This study used 69 pairs of monozygous twins to investigate possible dietary, biochemical, and anthropometric determinants of kallikrein that could result in this high spouse correlation. Urinary sodium and potassium excretion differences were significantly related to kallikrein differences, with urinary potassium having the strongest relationship ($r = 0.46$, $P = .0001$). Urinary pH ($r = 0.23$, $P = .03$) and systolic blood pressure ($r = -0.25$, $P = .03$) differences were associated with urinary kallikrein excretion differences independently of urinary potassium. Information on nutrients was obtained from a dietary food frequency questionnaire that ascertains usual intake over the last 5 years. Kallikrein differences between monozygous twins were not explained by differences in nutrient intake as measured by this questionnaire. Therefore, urinary potassium and pH probably represent the more acute effects of recent dietary sodium and potassium intake on urinary kallikrein levels. Urinary potassium, pH, and systolic blood pressure differences explained 34% of the difference in kallikrein levels between monozygous twins. The significant difference in systolic blood pressure between twins, even after controlling for electrolyte excretion differences suggests an additional unmeasured environmental variable that is associated with decreased kallikrein excretion and elevated blood pressure. Am J Hypertens 1993;6:226–233

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Urinary kallikrein excretion has been related to hypertension and increased blood pressure, with decreased levels of urinary kallikrein excretion in those with hypertension or a family history of hypertension.[1–9] Levels of excretion are also familial, with high cross-sectional and longitudinal family correlations.[10–12] Evidence for a single gene with large effects on kallikrein excretion has been found in both rats and humans.[9,13] From human data, the percent of the total variance of kallikrein explained by the major gene was estimated at 51%, with 27% of the variance being due to polygenic effects.[9] The remaining 22% percent was attributed to random effects, although a common environment component was not included in the genetic analysis.

In spite of the high genetic control of kallikrein excretion, there appears to be a large common environment influence as indicated by high spouse-spouse correlations of around 0.40.[12] The present study investigates whether environmental factors can be identified from

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dietary, biochemical, or anthropometric variables obtained from genetically identical monozygous (MZ) twins by relating differences in these variables to the differences in kallikrein excretion.

METHODS

The white, male monozygous twins used in this study were originally part of a study of diet and sex hormones described in a previous publication.[14] They were ascertained from Utah birth certificates and ranged in age from 22 to 66 years. Of the 77 MZ twin pairs used in the previous dietary study,[15] eight had one of the twins with missing kallikrein values, leaving 69 twin pairs for inclusion in these analyses. The twins were verified to be MZ twins by examining up to 22 polymorphic genes, which provided a 99.5% probability of correct classification.[14] None of the twins had coronary heart disease or diabetes, while 10 individuals had diagnosed hypertension.

Dietary data were obtained using a quantitative food frequency questionnaire to measure usual intake over the past 5 years, as described by Slattery et al.[15] These data were obtained by trained interviewers using NASCO food models and included information on the amount, frequency, and methods of food preparation for over 250 food items. Nutrient intake data were derived from food information using the Utah State University Food Composition Data Bank. Additional details can be found in Slattery et al.[15]

Anthropometric variables were obtained in the Cardiovascular Genetics clinic. Three skinfold thickness measurements were obtained at each site using Harpenden calipers and averaged. Triceps skinfold thickness was measured at the midpoint of the acromial process and elbow, subscapular skinfold thickness at the low tip of the scapula, diagonal to the midline of the spine, and suprailiac skinfold thickness 1 in. above the superior anterior iliac spine. Achilles tendon thickness was the smallest measurement taken. Circumferences were obtained using steel tape, and bone widths measured with sliding calipers (Pfister Import-Export Inc., Carlstadt, NJ). Chest girth was measured over the fourth rib at the pause between inspiration and expiration during normal breathing. Abdominal girth was taken at the midpoint between the 12th rib and the iliac crest. The maximal hip girth was measured as the maximal circumference over the buttocks. Arm girth was measured at the midpoint of the humerus while the arm was relaxed and while flexed. Also, arm girth was measured as the maximum girth along the humerus while flexed.

The mean of four blood pressures measured in a sitting position by an automated blood pressure device (Infrasonde SR-2 Automatic Blood Pressure Recorder, Sphygmetrics, Inc., Woodland Hills, CA) was used. Blood pressure reactivity to isometric exercise was measured by having each subject squeeze a handgrip dynamometer at 50% maximum for 2 min. Sitting blood pressures obtained after 1 and 2 min of this exercise were averaged and compared to the mean sitting blood pressure at baseline to obtain the blood pressure change due to isometric exercise.

Clinical chemistries were measured on fasting blood samples using an autoanalyzer (SMAC II Analyzer, Technicon Instruments Corp., Tarrytown, NY). Plasma total cholesterol,[16] triglycerides,[17] and high density lipoprotein (HDL) cholesterol[18] were obtained. Timed 12 h overnight urine volumes, pH, hematocrit, sodium, potassium, and creatinine were also obtained. Urinary kallikrein was measured by an adaptation of the method of Green and Shaw described previously.[19,20] Kallikrein concentrations were converted to amounts by multiplying by the urine volume and adjusting to a 12 h sample if collection was not a full 12 h. Plasma renin activity was measured by a radioimmunoassay which measures generated angiotensin I. Intraerythrocytic sodium was measured by atomic absorption spectroscopy.[21] Na-Li countertransport and the passive Li leak in erythrocytes were measured by the method of Canessa, as described by Smith.[22]

Alcohol usage was measured by the number of 12 oz cans of beer, 4 oz glasses of wine, or 1½ oz jiggers or shots of hard liquor consumed per week. Annual income level was a graded response to nine categories of income ranging from less than $5,000 to more than $50,000. The mean family income was in the $20,000 to $25,000 category. Education level was the actual number of years of education. The average number of times a month of church attendance was also requested as a measure of religious activity. Mean levels, standard deviations, and twin pair differences are given in Table 1.

Statistical Analysis Twins were sorted within pairs by lowest to highest kallikrein level. The differences between urinary kallikrein amounts for each twin pair were calculated along with differences for all other variables collected (twin with highest kallikrein minus twin with lowest kallikrein). Since MZ twins are identical genetically, correlating the intrapair difference in kallikrein with differences in other variables should identify nongenetic components of variables associated with the difference in kallikrein amounts. Tests for normality were done for all variables. Pearson correlations with kallikrein amounts were performed on all biochemical, anthropometric, and dietary data that were normally distributed. Spearman correlations were used for those variables not normally distributed. All variables significant at $P \leq .10$ were retained for use in a stepwise multiple regression. Both forwards and backwards regression were used to ensure that the same model was obtained.

Principal components analysis on the twin difference for each variable was done separately for the laboratory variables, anthropometrics, and dietary variables. Fac-

TABLE 1. MEANS AND STANDARD DEVIATIONS OF STUDY VARIABLES AND TWIN PAIR DIFFERENCES

Variable	Mean	Mean Twin Difference	P†
Age (year)	36.2 ± 10.7	0	
Systolic blood pressure (mm Hg)	122.8 ± 11.3	0.09 ± 11.2	.95
Diastolic blood pressure (mm Hg)	71.7 ± 10.2	0.01 ± 8.46	.99
Systolic BP change, isometric handgrip	17.7 ± 10.5	0.66 ± 14.3	.70
Diastolic BP change, isometric handgrip	17.1 ± 8.7	0.01 ± 11.3	.99
Family income (category 6 = $20-25,000)	6.70 ± 1.84	−0.40 ± 1.89	.10
Education level (year)	14.3 ± 2.3	0.27 ± 2.06	.29
Beer (12 oz cans/week)	2.33 ± 5.86	−1.26 ± 6.40	.11
Wine (4 oz glasses/week)	0.36 ± 1.43	−0.04 ± 1.11	.74
Liquor (shots or jiggers/week)	1.06 ± 3.15	0.76 ± 3.23	.06
Church attendance (times/week)	1.37 ± 0.48	−0.05 ± 0.42	.37
Anthropometrics			
Weight (kg)	78.8 ± 11.5	−0.55 ± 8.7	.60
Height (cm)	175.3 ± 5.9	−0.15 ± 2.97	.68
Sitting height (cm)	91.7 ± 3.6	−0.61 ± 2.62	.06
BMI (kg/m^2)	25.1 ± 3.2	−1.46 ± 25.0	.63
Triceps skinfold thickness (mm)	9.2 ± 3.7	−0.14 ± 3.00	.71
Subscapular skinfold thickness (mm)	16.9 ± 7.3	−0.93 ± 6.36	.23
Upper chest skinfold thickness (mm)	12.4 ± 5.9	−0.66 ± 5.46	.39
Abdominal skinfold thickness (mm)	20.5 ± 8.7	−0.90 ± 8.55	.45
Suprailiac skinfold thickness (mm)	16.8 ± 8.0	−1.13 ± 6.43	.15
Chest circumference (cm)	93.3 ± 7.3	0.23 ± 5.71	.77
Abdominal circumference (cm)	87.0 ± 9.0	−0.18 ± 7.35	.84
Hip circumference (cm)	96.1 ± 8.0	0.01 ± 7.55	.99
Midcalf circumference (cm)	37.4 ± 2.8	0.35 ± 2.54	.26
Arm girth, midhumerus, relaxed (cm)	31.4 ± 2.8	0.04 ± 2.23	.88
Arm girth, midhumerus, flexed (cm)	32.2 ± 3.1	−0.09 ± 2.36	.75
Arm girth, maximum, flexed (cm)	32.5 ± 3.1	0.01 ± 2.28	.97
Frame size (Category 1 = small, 6 = extra large)	4.38 ± 0.91	−0.03 ± 0.79	.76
Wrist diameter (cm)	6.76 ± 0.35	0.02 ± 0.21	.52
Knee width (cm)	9.92 ± 0.60	−0.04 ± 0.59	.59
Ankle width (cm)	7.13 ± 0.41	0.05 ± 0.41	.35
Achilles tendon thickness (mm)	15.7 ± 2.8	−0.06 ± 2.32	.83
Plasma			
Na (mmol/L)	140.6 ± 1.9	−0.16 ± 1.78	.46
K (mmol/L)	4.48 ± 0.35	0.04 ± 0.40	.45
CO_2 (mEq/L)	24.6 ± 1.7	−0.32 ± 1.95	.18
Blood urea nitrogen (mg/dL)	14.5 ± 3.7	0.60 ± 3.57	.17
Glucose (mg/dL)	99.8 ± 7.5	−0.26 ± 8.10	.79
Creatinine (mg/dL)	1.08 ± 0.1	−0.003 ± 0.12	.84
Uric acid (mg/dL)	6.26 ± 1.10	−0.14 ± 1.01	.26
Calcium (mg/dL)	9.53 ± 0.35	0.01 ± 0.33	.74
PO_4 (mg/dL)	2.94 ± 0.48	0.04 ± 0.51	.48
Total protein (g/dL)	7.04 ± 0.39	0.06 ± 0.35	.17
Albumin (g/dL)	4.59 ± 0.24	0.02 ± 0.21	.38
Total cholesterol (mg/dL)	197.5 ± 38.3	−2.26 ± 24.7	.45
Triglyceride (mg/dL)	121.8 ± 92.7	−20.9 ± 66.3	.01
HDL cholesterol (mg/dL)	43.9 ± 9.3	1.13 ± 6.58	.16
Plasma renin activity (ng/mL/h)	4.58 ± 4.30	0.44 ± 3.99	.40
Intraerythrocytic Na (mmol/L)	7.0 ± 1.3	−0.13 ± 0.86	.23
Na-Li countertransport (mmol/L cells/h)	0.29 ± 0.11	−0.01 ± 0.07	.47
Passive Li leak (10^3/h)	15.75 ± 5.27	−0.53 ± 3.80	.26
Hematocrit	47.6 ± 3.25	−0.24 ± 2.90	.50

TABLE 1. MEANS AND STANDARD DEVIATIONS OF STUDY VARIABLES AND TWIN PAIR DIFFERENCES *(Continued)*

Variable	Mean	Mean Twin Difference	P†
Urine			
Urine kallikrein amount (TAME U/12 h)	1.57 ± 1.33	0.83 ± 1.09	.0001
Urinary kallikrein/creatinine ratio	0.01 ± 0.07	0.001 ± 0.003	.002
Na amount (mg/12 h)	2069 ± 1049	385 ± 1287	.02
Na/creatinine ratio	3.6 ± 12.2	0.20 ± 1.96	.40
K amount (mg/12 h)	1067 ± 549	348 ± 704	.0001
K/creatinine ratio	1.8 ± 4.8	0.28 ± 1.27	.08
Creatinine concentration (mg/dL)	145.5 ± 64.9	12.1 ± 85.1	.25
Volume (mL)	694 ± 328	36.1 ± 431	.49
Specific gravity	1.02 ± 0.01	0.002 ± 0.008	.05
pH	6.00 ± 0.49	0.13 ± 0.63	.11
Collection time (h)	11.9 ± 0.6	0.03 ± 0.85	.78
Diet			
Total calories (kcal)	3525 ± 1501	32.9 ± 1471.5	.85
Protein (g)	161 ± 75	−2.94 ± 75.7	.75
Fat (g)	157 ± 75	0.36 ± 77.4	.97
Carbohydrate (g)	363 ± 159	13.3 ± 150.8	.47
Protein (% of calories)	18.2 ± 2.8	−0.24 ± 3.58	.58
Fat (% of calories)	39.6 ± 5.2	−0.06 ± 5.95	.94
Carbohydrate (% of calories)	41.7 ± 8.1	0.73 ± 8.27	.47
Saturated fatty acids (g)	59.0 ± 29.4	1.50 ± 30.0	.68
Monounsaturated fatty acids (g)	56.5 ± 28.8	0.25 ± 29.0	.94
Polyunsaturated fatty acids (g)	24.2 ± 11.9	−0.86 ± 13.7	.61
Cholesterol (mg)	713 ± 348	24.7 ± 319.2	.53
Crude fiber (g)	7.3 ± 3.8	0.39 ± 3.81	.40
Neutral detergent fiber (g)	16.3 ± 9.6	0.62 ± 10.7	.63
Ash (g)	27.2 ± 11.4	0.99 ± 11.2	.47
Calcium (mg)	1468 ± 690	51.3 ± 755	.58
Phosphorous (mg)	2437 ± 997	3.4 ± 1025	.98
Sodium (mg)	4662 ± 2065	180 ± 2128	.49
Potassium (mg)	4703 ± 1961	199 ± 1965	.41
Iron (mg)	25.2 ± 12.5	1.04 ± 12.8	.50
Copper (mg)	3.2 ± 1.3	0.07 ± 1.47	.69
Zinc (mg)	24.7 ± 12.0	−0.54 ± 12.5	.72
Vitamin E (mg)	12.3 ± 6.0	0.38 ± 6.93	.65
Selenium (μg)	251 ± 116	−16.44 ± 132.2	.31
Cadmium (μg)	77.6 ± 32.2	0.93 ± 36.6	.83
Thiamine (mg)	2.4 ± 1.1	0.08 ± 1.12	.54
Vitamin A (IU)	12386 ± 8562	972 ± 9045	.38
Riboflavin (mg)	3.3 ± 1.4	0.14 ± 1.49	.43
Niacin (mg)	38.4 ± 19.3	−0.55 ± 19.8	.82
Vitamin C (mg)	159 ± 83	19.3 ± 93.9	.10
Caffeine (mg)	211 ± 501	9.48 ± 211.2	.71
Theobromine (mg)	33.3 ± 42.7	−7.09 ± 59.1	.33
Saccharin (mg)	107 ± 167	−21.3 ± 176.7	.32
Nitrite (mg)	1.4 ± 1.2	0.12 ± 1.71	.57
Nitrate (mg)	108 ± 71	2.05 ± 77.8	.83
Trace nitrite (g)	53.4 ± 76.2	0.57 ± 56.9	.93
Trace nitrate (g)	491 ± 250	36.8 ± 258.4	.24

* *Differences calculated as twin with higher minus twin with lower kallikrein level.*
† *Significance of test for mean intrapair difference being equal to zero.*

tors from each of the three analyses with eigenvalues greater than one were retained and scores obtained for each twin pair. Kallikrein differences were then regressed on the factors obtained from these three principal components analyses in a forwards and backwards stepwise regression as described above.

RESULTS

As can be seen from Table 1, a large number of dietary, anthropometric, and biochemical variables were measured in this study. Analysis of these variables was done because a previous study which used a more hypothesis oriented approach to variable selection failed to find the reason for the high spouse correlation for urinary kallikrein levels.[12] Table 1 shows that urinary kallikrein levels were significantly different between monozygous twins. Urine potassium and sodium levels were also different between twins. However, none of the nutrient or anthropometric measurements differed between twins. Plasma triglyceride levels and urine specific gravity were the other two variables that differed significantly between twins.

Table 2 shows the significant univariate Pearson or Spearman correlation coefficients for each variable difference with the difference in the amount of urinary kallikrein excreted over 12 h between twins. The strongest correlations were with urinary excretion variables, including sodium and potassium excretion, either as amounts or as ratios dividing by urinary creatinine concentration, pH, and specific gravity. The only dietary variables that were correlated with kallikrein excretion differences were vitamin A, saccharin, and beer intake differences. There were no anthropometric measurements with a significant correlation, while HDL cholesterol and blood urea nitrogen were the two significant lab variables. Systolic blood pressure differences were inversely correlated with kallikrein excretion differences. The significance of these correlations was not adjusted for multiple comparisons because of the exploratory nature of this study, and some of these correlations could arise by chance at the $P = .10$ level. The nonsignificant correlations for five other variables are shown, so that the correlations of dietary, plasma, and urine electrolytes, and diastolic blood pressure with kallikrein can be compared.

When the significant variables were included in either a forwards or backwards stepwise regression the same final model was obtained, as shown in Table 3. Twin differences in urinary pH, urinary potassium amount, and systolic blood pressure were significantly associated with twin differences in urinary kallikrein. Differences in these three variables explained 34% of the kallikrein difference variance between MZ twins. None of the other variables were close to being significant with urinary potassium in the model, with the closest variable being urinary specific gravity ($P = .24$). If urinary potassium excretion was not allowed to enter the model, no other variables besides urinary pH and systolic blood pressure entered.

Since many of the variables in each of the major variable groups are highly correlated, we also performed a principal components analysis on the differences of each of the variables except kallikrein levels. Combining correlated variables into independent factors might

TABLE 2. CORRELATION COEFFICIENTS OF STUDY VARIABLE TWIN DIFFERENCES WITH URINARY KALLIKREIN DIFFERENCES

Variables	Correlation Coefficient	*P*
Systolic blood pressure*	−0.31	.009
Urine K amount*	0.46	.0001
Urine Na amount	0.30	.01
Urine K/urine creatinine concentrations	0.40	.0006
Urine Na/urine creatinine concentrations	0.20	.09
Urine pH	0.24	.04
Urine specific gravity*	0.20	.09
Dietary vitamin A	0.23	.06
Dietary saccharine	−0.24	.04
Beer intake	−0.27	.03
Plasma blood urea nitrogen*	0.26	.03
Plasma HDL cholesterol*	0.20	.09
Nonsignificant Variables		
Diastolic blood pressure*	−0.14	.26
Dietary Na*	−0.11	.36
Dietary K*	0.01	.94
Plasma Na*	−0.19	.12
Plasma K*	0.06	.61

* *Pearson correlation coefficient. Others are Spearman correlation coefficients.*

TABLE 3. FINAL MULTIVARIATE REGRESSION MODEL OF KALLIKREIN DIFFERENCES BETWEEN MONOZYGOUS TWIN PAIRS AND OTHER VARIABLE DIFFERENCES

Variable Difference	Standardized Regression Coefficient	Proportion of Explained Variance*	P
Urine K amount	0.41	23%	.0001
Systolic blood pressure	−0.25	6%	.03
Urine pH	0.23	5%	.03

** Proportion of additional variance after previously listed variables are in the model.*

allow better description of the kallikrein differences within twin pairs. Table 4 presents the four most significant factors from three different factor analyses on the three categories of variables along with the four highest loading (by absolute value) variables on each factor. The factor scores in Table 4 are not correlations with kallikrein level, but correlations of the twin differences of that variable with the factor itself, which consists of all of the biochemical variables excluding kallikrein. Stepwise regressions of kallikrein differences on these factors showed that only one factor, the total calorie factor, was significant ($r = -0.26$, $P = .04$). Total calories, ash, phosphorous, and potassium intake had approximately the same loadings on this factor. Factor 1 of the biochemistry variables included urinary potassium amount as the fourth highest loading variable. However the association of this factor with twin kallikrein differences was not significant, in spite of the high urinary potassium loading. This may have been because the three major variables associated with this factor, plasma calcium, albumin, and protein, were not related to kallikrein levels. Factor 2 was also nonsignificant, even though all of the highest four loading variables were sodium or potassium related measurements. This result may again suggest that urinary potassium is the single most important biochemical determinant of kallikrein level, since defining a factor in terms of the combination of urinary sodium, potassium, and their ratios to creatinine made the statistical significance disappear. Therefore, our use of the multiple regression model in this study seems to be adequate for identifying important associations with

TABLE 4. HIGHEST LOADING VARIABLE DIFFERENCES ON FACTORS DETERMINED SEPARATELY ON DIETARY, ANTHROPOMETRIC AND BIOCHEMISTRY VARIABLE DIFFERENCES

Factors	Variable 1	Variable 2	Variable 3	Variable 4
		Dietary		
Factor 1	Total calories	Ash	Phosphorous	Potassium
56%*	0.98†	0.98	0.96	0.95
Factor 2	% Carbohydrate	% Fat	% Protein	Neutral detergent fiber
10%	0.91	−0.77	−0.67	0.45
Factor 3	Saccharin	Total nitrite	Theobromine	Calcium
5%	0.50	−0.46	0.45	0.40
Factor 4	Theobromine	% Protein	Nitrite	Saccharin
4%	0.54	−0.53	0.44	0.42
		Anthropometric		
Factor 1	Weight	Abdominal girth	Body mass index	Arm girth, relax
53%	0.88	0.87	0.84	0.84
Factor 2	Subscapular skinfold	Arm girth, max. flex	Arm girth, flex	Suprailiac skinfold
9%	−0.44	−0.43	−0.42	0.40
Factor 3	Frame size	Wrist circumference	Suprailiac skinfold	Weight
8%	0.77	0.54	−0.27	−0.19
Factor 4	Achilles tendon	Triceps skinfold	Subscapular skinfold	Arm girth, flexed
7%	0.61	0.46	0.31	−0.27
		Biochemistry		
Factor 1	Calcium	Albumin	Total protein	Urinary K amount
16%	0.77	0.72	0.60	0.56
Factor 2	Urinary K/creatinine	Urinary K amount	Urinary Na/creatinine	Plasma Na
11%	−0.56	−0.53	−0.52	0.51
Factor 3	Na-Li countertransport	Glucose	Blood urea nitrogen	PO_4
10%	0.72	0.64	−0.45	−0.42
Factor 4	Uric acid	HDL cholesterol	Triglyceride	Albumin
9%	0.54	−0.53	0.47	−0.43

** Percent of total variance explained by this factor.*

† Factor loading coefficients of the four variables that had the highest correlation with the overall factor. The biochemistry factor analysis did not include the kallikrein levels as a variable.

twin kallikrein differences among a large number of correlated variables.

DISCUSSION

The variable that explained the greatest difference in 12 h urinary kallikrein amounts between MZ twins was the difference in the amount of urinary potassium excreted. In a steady state, urinary potassium excretion is an indication of dietary potassium intake. Since we only measured kallikrein and potassium excretion from one 12 h urine sample, it is possible that short-term effects due to overnight fasting or stress related to a clinical exam might influence potassium excretion independently of diet. Aldosterone, which is correlated with kallikrein excretion and is an important regulator of potassium excretion, might be influenced by these short-term effects, giving rise to the results seen here. While it is believed that changes in aldosterone require more than 1 day to influence kallikrein excretion,[23] it or some other factor could alter both urinary kallikrein and urinary potassium excretion.

While dietary intake would seem to be the most logical explanation influencing urinary potassium differences between twins, dietary potassium differences between twins did not correlate with urinary kallikrein differences. The food frequency questionnaire measured usual intake of potassium over the past 5 years. Because dietary potassium intake differences between twins, as measured by this questionnaire, did not correlate with kallikrein differences, urinary potassium excretion appears to be a more precise measurement of potassium intake as far as its relationship to kallikrein is concerned. Perhaps a 3 day food record would have increased the precision of the estimate of current dietary intake and provided a significant association. This may be suggested by the high correlation of dietary potassium with dietary factor 1, which was significantly related to urinary kallikrein levels. The reparameterization by factor analysis appeared to either provide more precision for the dietary potassium component of the factor than for dietary potassium alone, or added information using the other three variables with high loadings on this factor: total calories, dietary ash, or dietary phosphorous.

Other studies have shown that dietary potassium influences urinary potassium and kallikrein excretion, as well as decreases in blood pressure. Dietary potassium supplementation for 4 weeks increased urinary kallikrein levels 52% and urinary potassium levels 124%, with a correlation of the change in the two variables of $r = 0.50$, $P < .0005$.[24] Blood pressure was also reduced in this study by 6/3 mm Hg. Another study showed increased dietary potassium stimulated urinary kallikrein release in both normotensive and hypertensive patients.[25] The release was less in the patients with more severe hypertension than those with mild hypertension, suggesting decreased effectiveness of the kallikrein system in the more severe hypertensive patients. If a large proportion of the more severe hypertensive patients had the gene for low urinary kallikrein levels,[9] while the mild hypertensive patients had a lower frequency of this gene, this may explain the resistance to a dietary potassium effect.

Another study investigated the effects of both a reduced and increased potassium diet.[26] A low potassium diet (25 mEq/day) decreased kallikrein excretion by 46% and 31% in normotensive and hypertensive patients, respectively. A high potassium diet (185 mEq/day) increased urinary kallikrein excretion 77% and 58% in the same two groups of patients. Changes in urinary aldosterone paralleled the changes in kallikrein excretion suggesting that the dietary potassium effects on kallikrein were mediated through changes in aldosterone.

This study also showed that some other unmeasured factor(s) are related to the correlation of kallikrein with blood pressure. Within twin pairs, the twin with lower levels of urinary kallikrein had higher systolic blood pressure. This association appeared to be independent of the measured factors in this study and was found even though, on average, there was no significant blood pressure difference between twins. The environmental factors could act by themselves or interactively with an underlying genetic susceptibility. These other factors are likely responsible for the spouse correlations found in an earlier study,[12] since adjusting for urinary potassium excretion had little effect on the spouse correlations. Whatever these factors are, this result shows that urinary kallikrein differences between monozygous twins are significantly related to blood pressure differences. Whether the factors that cause twin differences in kallikrein are unmeasured environmental factors, environmental interactions with kallikrein genotype, or some measured factor that was not found to be significant because the statistical modeling did not adequately describe the actual underlying pathophysiology remains to be determined.

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