Association of circulating uric acid and angiotensin-(1-7) in relation to higher blood pressure in adolescents and the influence of preterm birth

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Abstract

Elevated serum uric acid increases the risk of hypertension, and individuals born preterm have higher blood pressure (BP) and uric acid, but the mechanisms remain unclear. Preclinical studies demonstrate uric acid increases BP via increased renin-angiotensin system (RAS) expression, especially angiotensin (Ang) II, but the association of uric acid with Ang-(1–7) is unknown. Ang-(1–7), an alternative RAS product, counteracts Ang II by stimulating sodium excretion, vasodilation, and nitric oxide, thus contributing to lower BP. Plasma Ang-(1–7) is lower in preterm-born adolescents. We hypothesized uric acid is associated with a higher ratio of Ang II to Ang-(1–7) in plasma, especially in preterm-born adolescents. We measured BP, serum uric acid, and plasma RAS components in a cross-sectional analysis of 163 14-year-olds (120 preterm, 43 term). We estimated the associations between uric acid and the RAS using generalized linear models adjusted for sex, obesity, sodium intake, and fat intake, stratified by birth status. Uric acid was positively associated with Ang II/Ang-(1–7) (adjusted β (aβ): 0.88 mg/dl, 95% CI 0.17 to 1.58), plasma renin activity (aβ: 0.32 mg/dl, 95% CI 0.07 to 0.56), and aldosterone (aβ: 1.26 mg/dl, 95% CI 0.18 to 2.35), and inversely with Ang-(1–7) (aβ: −1.11 mg/dl, 95% CI −2.39 to 0.18); preterm birth did not modify these associations. Higher Ang II/Ang-(1–7) was associated with higher uric acid in adolescents. As preterm birth is associated with higher BP and uric acid, but lower Ang-(1–7), the imbalance between uric acid and Ang-(1–7) may be an important mechanism for the development of hypertension.

INTRODUCTION

Cardiovascular disease is the leading cause of mortality worldwide [1]. Hypertension, the leading cause of death among all cardiovascular risk factors, affects over 100 million adults in the U.S. [2] Prematurity is an emerging risk factor for both hypertension and cardiovascular disease, but the mechanisms of how it contributes are not known [3]. Uric acid, a by-product of purine metabolism, predicts the development of hypertension in healthy adults [4]. We previously showed that serum uric acid levels were higher in adolescents born preterm and correlate with higher blood pressure (BP) in preterm-born adolescents as compared to adolescents born at term [5]. However, the specific mechanisms by which uric acid contributes to hypertension remain elusive.

Preclinical studies suggest that uric acid increases BP in part by activating the renin-angiotensin system (RAS), in particular the angiotensin-converting enzyme (ACE) – angiotensin (Ang) II – Ang II type 1 receptor pathway [6]. The RAS also may be susceptible to early-life programming events that upregulate the ACE – Ang II – Ang II type 1 receptor pathway and downregulate the ACE2 – Ang-(1–7) – Mas receptor axis [7]. Ang-(1–7) in part attenuates Ang II-mediated increased BP and inflammation via nitric oxide-dependent vasodilation and reduced oxidative stress, thus reduction of Ang-(1–7) may promote development of hypertension and cardiovascular disease [8]. We previously showed that perinatal programming events such as preterm birth are associated with higher BP and elevated plasma aldosterone and Ang II but lower plasma Ang-(1–7) during adolescence [9,

10]. However, the association of uric acid with the RAS is incompletely characterized clinically [11], and no prior experimental or clinical studies have investigated the association between uric acid and Ang-(1–7). Therefore we hypothesized that higher serum uric acid levels and higher BP would be associated with a higher ratio of Ang II/Ang-(1–7) in the plasma in a cohort of adolescents, and that these associations would be magnified in adolescents born preterm compared to those born term.

METHODS

Participants and design

Subjects were recruited from a prospective birth cohort of 193 individuals born preterm between January 1, 1992 and June 30, 1996 at a regional perinatal center (Forsyth Medical Center in Winston Salem, NC). The cohort was evaluated at 14 years of age in a series of three study visits. Inclusion criteria in the preterm cohort were singleton birth, birth weight <1500 grams, and follow-up clinical data through at least 1 year corrected age. The term-born subjects were recruited via newspaper advertisements and word of mouth; inclusion criteria were birth at the same perinatal center, birth weight 2500 g, gestational age 37 weeks, and no antenatal steroid exposure. Exclusion criteria for both groups were history of major genetic syndromes or congenital anomalies or being wards of the state. The Institutional Review Boards of Wake Forest School of Medicine and Forsyth Medical Center approved the study. Parents/guardians and subjects provided written informed consent and assent and were compensated.

Data collection

A research nurse reviewed patients' medical records and research databases, and questionnaires were administered to parents/guardians to obtain maternal and subject birth characteristics; presence of maternal hypertensive pregnancy was determined via questionnaire for term-born participants. One preterm-birth subject was missing maternal hypertensive pregnancy data from the medical record and thus was assigned the response recorded from the questionnaire (kappa = 0.78 for agreement between the medical record and questionnaire in the preterm-birth cohort). Subjects were classified as small for gestational age if birth weight was <10th percentile for gestational age and sex [12].

In the current analysis, we report the data collected at the third study visit when blood samples were collected. Study personnel were blinded to preterm birth status when assessing outcomes. Adolescent demographics were recorded (including parent/guardian-reported race as black or non-black), height and weight were measured, and body mass index was calculated. We categorized subjects as having obesity if the body mass index was 95th percentile for age and sex [13]. Subjects privately rated their sexual maturity using a questionnaire (scale of 1–5); we report the percentage of subjects with a score of 5 [14]. Registered dietitians collected 24-hour food recalls and 3-day food records from which mean daily sodium intake and mean daily fat intake (as a percentage of total caloric intake) were derived and averaged between the two dietary measures. We defined high-sodium intake as mean daily sodium intake >2300 mg and high-fat intake as mean daily fat intake >35% of total caloric intake according to U.S. Department of Agriculture guidelines [15].

Subjects' BP was measured according to established guidelines by trained research staff using a mercury manometer and an appropriately sized cuff [16]. Each subject was seated quietly for at least five minutes with the arm fully supported. The averages of three systolic and diastolic BP measurements (taken 1 minute apart) were recorded, and BP z-scores were calculated according to age, sex, and height [17]. We defined high BP as a systolic or diastolic BP 120/80 mmHg [18] and further categorized it as i) elevated BP if 120 to 129/<80 mmHg; ii) stage 1 hypertension if 130 to 139/80–89 mmHg; and iii) stage 2 hypertension if 140/90 mmHg, according to the 2017 Pediatric High Blood Pressure Clinical Practice Guidelines [19].

Laboratory measurements

Laboratory methods including measurements of the RAS and uric acid have been described in detail previously [5, 10]. In brief, blood samples were collected with the subjects seated to measure Ang II, Ang-(1–7), plasma renin activity (PRA), aldosterone, and uric acid. Samples intended for peptide analysis were immediately collected in a tube containing an inhibitor cocktail to prevent exogenous generation or metabolism of the peptides. Ang II, Ang-(1–7), PRA, and aldosterone were measured using separate radioimmunoassays that we have previously validated against mass spectrometry [20], while serum uric acid was determined by uricase. We calculated the Ang II/Ang-(1–7) ratio. Sample results below the lower limit of detection were divided by the square root of two, according to a well-validated technique we have employed previously in this cohort [10, 21].

Statistical analyses

The outcomes reported in this analysis are secondary outcomes of the main study. Data were described using frequencies and measures of central tendency and dispersion, including means with *SD* and medians with interquartile range. We used chi-square test, Fisher's exact test, t-test, and Wilcoxon rank-sum test for between-group comparisons; the pooled method was used for t-tests with equal group variances while the Satterthwaite method was used for t-tests with unequal group variances. We used Pearson and Spearman coefficients to assess correlations between continuous variables. A two-sided alpha level <0.05 was considered statistically significant. We estimated the association of uric acid with the RAS and, as a secondary analysis, the association of the RAS with BP using generalized linear models. We utilized directed acyclic graphs to assess for potentially confounding factors according to the literature *a priori* and identified the following minimally sufficient adjustment sets for inclusion in the models: i) sex, obesity, sodium intake, and fat intake for the uric acid – RAS models and ii) sex, race, maternal hypertensive pregnancy, and obesity for the RAS – BP models [9, 22–24]. We *a priori* assessed for effect modification by preterm birth status by including interactions terms in the models and stratified analyses if suggestive of an interactive effect (interaction term p value <0.2), based on our prior work [10]. We did not adjust for multiple comparisons. For the models, distributional characteristics of the outcome variables were improved with natural logarithmic transformation as indicated. We used Enterprise Guide software, Version 7.11 of the SAS System for Windows for all analyses (SAS Institute Inc., Cary, NC).

Code availability

The specific SAS code used in generating the results of this paper are available upon reasonable request.

RESULTS

Of the 193 preterm-birth subjects successfully enrolled, five were further excluded (Figure 1). At the third visit, 177 subjects were evaluated; in the present analysis 120 subjects were included. Among the 52 enrolled term-born subjects, 43 were included in the present analysis.

Comparisons of the clinical characteristics between the preterm and term-birth groups are shown in Table 1. The preterm-birth cohort had higher proportions of maternal hypertensive pregnancy, maternal smoking during pregnancy, and Cesarean section delivery. There was no difference in the proportion of small for gestational age between the two groups. At age 14 years, the preterm-birth cohort was shorter, had a greater proportion of Medicaid use, and had a higher-fat diet.

Compared to their term-born peers, preterm-born adolescents had significantly higher mean SBP, SBP z-score, and DBP z-score and a greater proportion of high BP (Table 2). Preterm-born individuals also had higher DBP but this did not reach statistical significance ($p = 0.09$). The preterm-birth cohort had significantly higher mean serum uric acid levels and lower median plasma Ang II and Ang-(1–7) levels but higher median plasma Ang II/Ang-(1–7) compared to their term-born peers. PRA and aldosterone did not differ between the two groups.

Association between uric acid and the renin-angiotensin system

We evaluated the association of uric acid with components of the RAS. On unadjusted analyses, higher uric acid was associated with lower Ang-(1–7) and higher Ang II/Ang-(1–7), PRA, and aldosterone (Table 3, Figure 2), though the association with aldosterone was not statistically significant (unadjusted $p = 0.17$). After adjusting for sex, obesity, sodium intake, and fat intake, uric acid was associated with Ang II/Ang-(1–7) (adjusted β: 0.88 mg/dl, 95% CI 0.17 to 1.58 mg/dl), PRA (adjusted β: 0.32 mg/dl, 95% CI 0.07 to 0.56 mg/dl), and aldosterone (adjusted β: 1.26 mg/dl, 95% CI 0.18 to 2.35 mg/dl). Adjusted analysis attenuated the uric acid – Ang-(1–7) association (adjusted β: –1.11 mg/dl, 95% CI –2.39 to 0.18 mg/dl, $p = 0.09$). Uric acid was not statistically significantly associated with Ang II on unadjusted or adjusted analyses. Stratification by preterm birth status revealed that preterm birth did not modify the magnitude of these associations.

Association between the renin-angiotensin system and blood pressure

We evaluated the association between the RAS and BP; Ang II/Ang-(1–7) values were natural log transformed. On unadjusted analyses, higher Ang II/Ang-(1–7) was associated with higher SBP z-score (unadjusted β: 0.14, 95% CI –0.006 to 0.28) and higher aldosterone was associated with higher DBP (unadjusted β: 0.18 pmol/l, 95% CI –0.0003 to 0.36 pmol/l), though these were not statistically significant ($p = 0.06$ and $p = 0.05$, respectively).

Adjustment for sex, race, maternal hypertensive pregnancy, and obesity attenuated these associations (Ang II/Ang-(1–7) – SBP z-score adjusted β: 0.05, 95% CI –0.1 to 0.2, $p = 0.5$; aldosterone – DBP adjusted β: 0.17 pmol/l, 95% CI –0.01 to 0.35 pmol/l, $p = 0.07$). Ang II and Ang-(1–7) individually as well as plasma renin activity were not statistically significantly associated with the BP measures. Preterm birth did not modify the strength of these associations.

DISCUSSION

We demonstrated that higher serum uric acid levels were associated with higher Ang II/Ang-(1–7) in the circulation of 14-year-old adolescents. Our results support the possibility that uric acid may contribute to higher BP and development of hypertension in part by suppressing Ang-(1–7) in the circulation (Figure 3). Whether there is direct Ang-(1–7) suppression by uric acid or by other mechanisms, higher uric acid in the setting of lower Ang-(1–7) may have greater consequences for increased BP. This may be of particular importance in individuals born preterm, as they demonstrate higher BP and a higher prevalence of high BP in adolescence compared to their term-born peers.

The higher BP evident in individuals born preterm may be due in part to alterations in uric acid metabolism that may differentially influence the RAS potentially as a consequence of perinatal programming events. We previously showed that the preterm-birth cohort has higher uric acid levels and a higher ratio of Ang II to Ang-(1–7) compared to their term-born peers, and which correlated with BP in a larger sample of the study population [5, 10]. The reasons for this are unclear but may be due to increased production or decreased renal excretion of uric acid [25]. Exogenous uric acid increases the expression of the precursor protein angiotensinogen, ACE, and Ang II in vascular endothelial cells and smooth muscle cells [6, 26]. Indeed, uric acid may induce a positive feedback pathway whereby increased local Ang II expression further increases oxidative stress, and oxidative stress then further stimulates the ACE – Ang II – Ang II type 1 receptor axis [20]. As alterations in either RAS pathway (i.e. increased Ang II or decreased Ang-(1–7) expression) can contribute to hypertension [27], uric acid may induce suppression of Ang-(1–7). However, the association of uric acid with the Ang-(1–7) pathway had not been evaluated previously. Our results suggest that uric acid-related Ang-(1–7) suppression, relative to Ang II, may be a novel mechanism contributing to hypertension. A possible explanation could be increased oxidative stress as a consequence of reduced nitric oxide production as well as attenuated scavenging of vascular reactive oxygen species resulting from the increased Ang II/decreased Ang-(1–7) [20, 26, 27]. This may occur even at normal circulatory concentrations of uric acid due to increased sensitivity to uric acid's actions that could reflect the loss of uric acid's and Ang-(1–7)'s antioxidant properties; however further investigation quantifying oxidative stress is warranted [28].

Uric acid may additionally contribute to hypertension via direct actions in the kidney, though the exact renal effects of uric acid are incompletely characterized [23]. Ang II increases sodium retention in part via activating sodium-retaining mechanisms in the kidney. Conversely, Ang-(1–7) stimulates natriuresis, and uric acid-related Ang-(1–7) suppression could increase the overall Ang II effect on sodium retention, as occurs in experimental

models of programmed hypertension [29]. We have demonstrated previously that our preterm-birth cohort has altered renal sodium handling and altered urinary RAS levels compared to their term-born peers [10, 30]. Additionally, chronic kidney disease is associated with hyperuricemia, and we have previously reported that our preterm-birth cohort has reduced though normal renal function compared to their term-born peers [18]. Further exploration of these renal mechanisms is warranted.

Our results suggest several interesting areas of further study. Both increased uric acid and Ang II have been implicated in salt sensitivity of BP, which is associated with hypertension and cardiovascular disease and is present in children born preterm [31, 32]. A short-term low-salt diet leads to increased circulating uric acid and reduced uric acid excretion; these effects are magnified in individuals with salt sensitivity of BP and may be driven by an activated RAS [33]. Further investigation in prospective and interventional studies is warranted to confirm these causative relationships and to fully evaluate whether these effects are of particular importance in individuals born preterm.

Despite encouraging experimental data and an abundance of epidemiologic evidence supporting the association of uric acid with hypertension, clinical trials investigating the use of uric acid-lowering medications to reduce BP in hypertensive patients have produced conflicting results. Although short-term treatment lowers BP and improves vascular function, the long-term effects of uric acid reduction/inhibition remain undescribed [34, 35]. The association between hyperuricemia and development of hypertension is greatest in younger individuals and those born preterm [34]. Moreover, the greatest reductions in BP in clinical trials occur in adolescents and young adults, possibly because this uric acid-RAS-BP mechanism is initially reversible [34, 36]. Consequently, there may be key developmental windows during which therapy to reduce uric acid levels could be most effective.

The strengths of our study include characterization of the RAS within a large cohort with comprehensive dietary information that included a high prevalence of high dietary salt intake. Our study's limitations include the cross-sectional analysis that precludes causative inference (in particular the temporal sequence of events and directionality related to changes in uric acid, the RAS, and BP) and the smaller sample size of term-born adolescents which likely decreased our power to detect statistically significant interactions by preterm birth status and may have contributed to the attenuated statistical significance of the uric acid – Ang-(1–7) association as well as the association of the RAS with BP. The current analyses are secondary outcomes of the original study, and the preterm and term-birth cohort sample sizes were based on power calculations for the primary outcomes. Preterm-term birth differences may be detectable as the subjects age. We did not measure 24-hour urine sodium or uric acid excretion or measure the precursor peptide angiotensinogen nor the peptidases neprilysin, ACE, or ACE2 in the blood.

In conclusion, we demonstrated that higher serum uric acid levels were associated with higher Ang II/ Ang-(1–7) in the circulation in adolescents. This is the first study to provide evidence supporting the concept that uric acid may contribute to increased BP by suppressing Ang-(1–7). This could be a key mechanism in the development of hypertension, though further investigation in clinical and mechanistic studies is warranted to better

delineate how these relationships may differ between individuals born preterm and those at term.

Acknowledgements

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SUMMARY TABLE

What is known about this topic

- Preterm birth, higher serum uric acid, and lower plasma angiotensin-(1–7) are associated with hypertension but the relationships among these factors are unclear.

What this study adds

- Higher uric acid is associated with a higher ratio of angiotensin II to angiotensin-(1–7) in the circulation, driven primarily by lower circulating angiotensin-(1–7).

- Uric acid-induced angiotensin-(1–7) suppression, or higher uric acid in the presence of lower angiotensin-(1–7) regardless of the mechanism, may contribute to the development of hypertension.
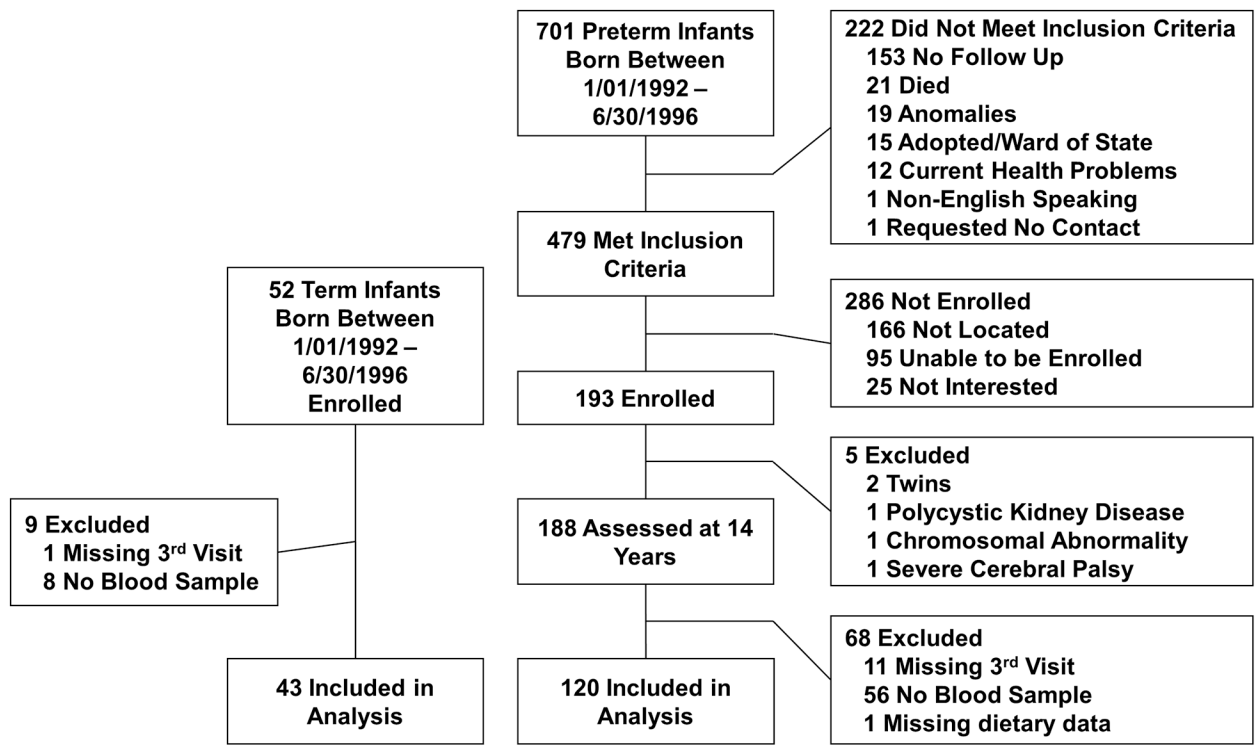
Fig. 1.
Study flow diagram
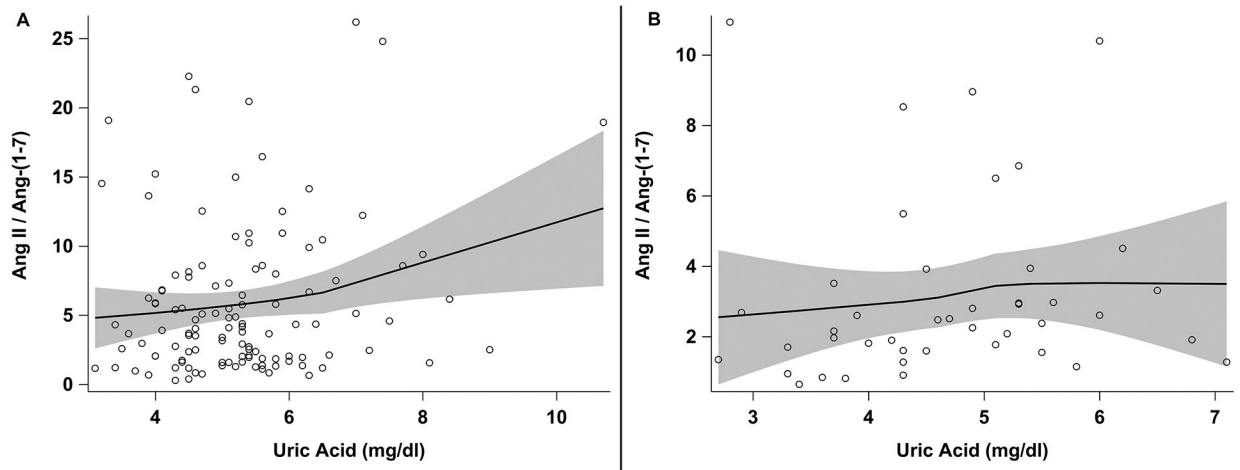
Fig. 2.
A-B Correlation between serum uric acid and plasma Ang II/Ang-(1–7) in preterm-born and term-born adolescents Loess fitted curves in black with confidence limits for mean predicted values in grey shading; individual data points and unadjusted generalized linear model regression coefficients with corresponding p values are provided. A: Preterm-birth cohort, unadjusted β (95% CI) 0.78 (−0.01, 1.56), $p = 0.05$. B: Term-birth cohort, unadjusted β (95% CI) 0.19 (−0.52, 0.9), $p = 0.6$. Ang, angiotensin.

Programming Event

↑ Uric Acid

↓ Ang-(1-7)

↑ Ang II ↑ NF-κB ↑ ERK ↑ ROS

↓ PI3K ↓ eNOS

Sodium Retention   **Vascular Inflammation**   **Cardiac Inflammation**

Hypertension Cardiovascular Disease
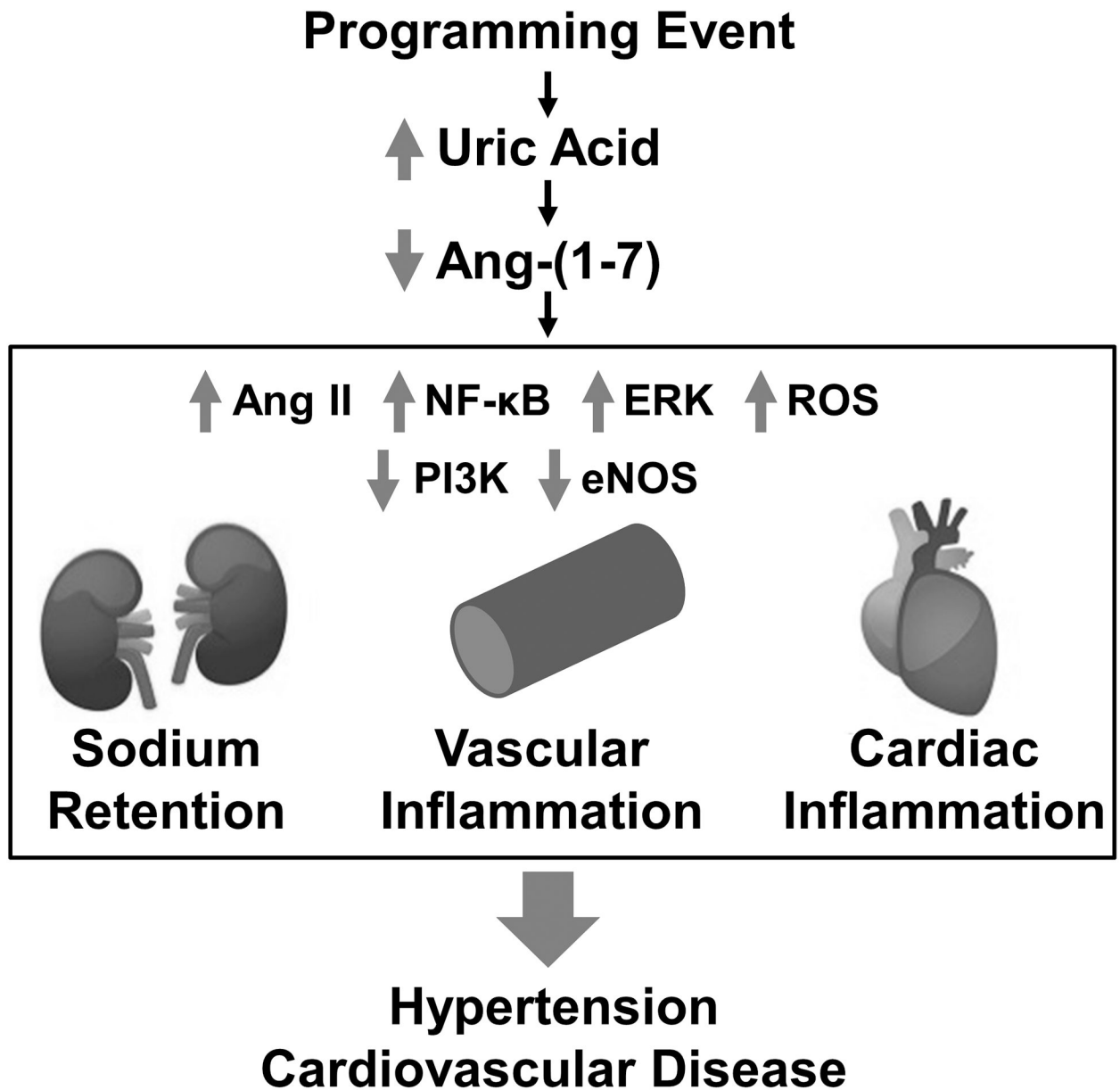
Fig. 3.
Conceptual diagram of the uric acid – Ang-(1–7) – BP association Programming events such as preterm birth may increase uric acid expression which then may suppress Ang-(1–7) expression but correspondingly increase Ang II expression. This in turn could lead to renal sodium retention and increased BP. In addition, Ang II-mediated increased oxidative stress, in part via upregulation of NF-κB and ERK and downregulation of PI3K leading to reduced eNOS but increased ROS, could increase inflammation in the kidneys, vasculature, and heart ultimately promoting development of hypertension and cardiovascular disease. Ang, angiotensin; BP, blood pressure; eNOS, endothelial nitric oxide synthase; ERK, extracellular regulated kinase; NF-κB, nuclear factor kappa enhancer of B cells; PI3K, phosphoinositide 3-kinase; RAS, renin-angiotensin system; ROS, reactive oxygen species.

Table 1.

Clinical characteristics of the preterm- and term-birth groups

	Preterm N = 120	Term N = 43
Perinatal		
Maternal hypertensive pregnancy	43 (36%)[*]	3 (7%)
Maternal smoking	22 (18%)[*]	1 (2%)
Cesarean section	63 (53%)[*]	7 (16%)
Gestational age, wk	27.8 (2.6)[*]	39.6 (1.1)
Birth weight, g	1055 (272)[*]	3455 (450)
Small for gestational age	12 (10%)	3 (7%)
Adolescent		
Female	70 (58%)	23 (53%)
Black	41 (34%)	17 (40%)
Height, cm	161.7 (9.5)[*]	168.0 (7.2)
Weight, kg	59.9 (15.6)	64.6 (16.0)
Body mass index, kg/m^2	21.6 [19.1, 25.9]	21.2 [19.3, 24.8]
Obesity	26 (22%)	5 (12%)
Sexual maturity rating = 5[a]	74 (62%)	26 (60%)
Current Medicaid use[b]	46 (39%)[*]	7 (16%)
Current smoker	2 (2%)	1 (2%)
Dietary intake		
Average daily sodium intake, mg	3644 [2654, 4888]	3487 [2893, 4466]
Average daily fat intake (% calories)	35.6 (5.8)[*]	32.6 (5.2)
High-salt diet	116 (97%)	41 (95%)
High-fat diet	86 (72%)[*]	19 (44%)

N (%), mean (*SD*), or median [IQR].

[*] *P* < 0.05 for preterm vs. term comparison via chi-square test or t-test.

[a] *N*=162 (119 preterm, 43 term);

[b] *N*=160 (117 preterm, 43 term).

Table 2.

Comparison of blood pressure, uric acid, and renin-angiotensin system components between the preterm- and term-birth groups

	Preterm *n* = 120	Term *n* = 43
Systolic blood pressure, mmHg	107.4 (10.1)[*]	103.7 (6.8)
Diastolic blood pressure, mmHg	61.3 (9.0)	58.7 (7.9)
Systolic blood pressure z-score[a]	−0.16 (0.92)[*]	−0.67 (0.64)
Diastolic blood pressure z-score[a]	−0.25 (0.84)[*]	−0.61 (0.73)
High blood pressure	16 (13%)[*]	1 (2%)
Elevated blood pressure	12 (10%)	1 (2%)
Stage 1 hypertension	3 (3%)	0 (0%)
Stage 2 hypertension	1 (1%)	0 (0%)
Uric acid (mg/dl)	5.3 (1.2)[*]	4.7 (1.1)
Ang II / Ang-(1–7)[b]	4.2 [2.0, 7.9][*]	2.4 [1.6, 3.5]
Ang II (pmol/l)[b]	21.5 [16.7, 32.1][*]	26.0 [18.4, 39.7]
Ang-(1–7) (pmol/l)	5.7 [2.2, 13.6][*]	12.8 [9.9, 16.0]
PRA (pmol Ang I/l/h)	2.3 [1.2, 3.2]	2.0 [1.3, 3.7]
Aldosterone (pmol/l)[c]	9.7 [5.3, 14.0]	7.8 [5.3, 14.5]

N (%), mean (*SD*), or median [IQR]. Ang, angiotensin; PRA, plasma renin activity.

[*] $P < 0.05$ for preterm vs. term comparison via Fisher's exact test, t-test, or Wilcoxon rank-sum test.

[a] *N*=161 (118 preterm, 43 term);

[b] *N*=162 (119 preterm, 43 term);

[c] *N*=162 (120 preterm, 42 term).

Table 3.

Association of uric acid with the renin-angiotensin system

Model	Crude β (95% CI)	Adjusted β (95% CI)
Ang II / Ang-(1–7)[a]	0.84 (0.21 to 1.46)	0.88 (0.17 to 1.58)
Ang-(1–7)	−1.18 (−2.27 to −0.09)	−1.11 (−2.39 to 0.18)
Plasma renin activity	0.25 (0.05 to 0.45)	0.32 (0.07 to 0.56)
Aldosterone[b]	0.64 (−0.28 to 1.56)	1.26 (0.18 to 2.35)

Generalized linear models, adjusted for sex, obesity, sodium intake, and fat intake. Estimates in mg/dl. Ang, angiotensin.

[a]N=162 (119 preterm, 43 term);

[b]N=162 (120 preterm, 42 term).