CLINICAL NEPHROLOGY – EPIDEMIOLOGY – CLINICAL TRIALS

Hypothesis: Uric acid, nephron number, and the pathogenesis of essential hypertension

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Background. Essential hypertension affects more than 25% of the world's population. Genetic, physiologic, and epidemiologic studies provide clues to its origins, but a clear understanding has been elusive. Recent experimental and clinical studies have implicated uric acid in the onset of essential hypertension.

Methods. In a retrospective chart review, we identified 95 children with confirmed, new onset hypertension, and evaluated the cause of hypertension and parental history of hypertension, birth weight, and serum uric acid. In an open-label, cross-over trial we treated 5 children with confirmed essential hypertension with allopurinol as single treatment agent, and screened for change in blood pressure by casual and ambulatory methods. In tissue culture experiments, we evaluated the effect of uric acid on glomerular endothelial cell function.

Results. Elevation of serum uric acid is related to the onset of essential hypertension in children, reduced birth weight, and endothelial dysfunction. Normalization of uric acid appears to ameliorate new onset essential hypertension.

Conclusion. These findings, combined with animal model data, support the hypothesis that uric acid has a key role in the pathogenesis of early onset essential hypertension, and may unify some of the disparate theories of the origins of essential hypertension.

Essential hypertension affects 25% of the world's population and is a major cause of stroke, congestive heart failure, end-stage renal disease, and myocardial infarction. Renal transplantation studies in animals and hu-

mans strongly suggest that the underlying cause resides in the kidney [1, 2]. Most evidence is consistent with Guyton's hypothesis [3] that at similar levels of blood pressure, individuals with essential hypertension have a physiologic defect in the efficiency of renal sodium excretion. It is likely that in some cases the defect is mediated by genetic alterations in the expression or regulation of transport mechanisms involved in sodium reabsorption or excretion [4]. Genetic linkage studies, however, reveal few significant genetic correlations with essential hypertension [5, 6], suggesting the genetic contributions to hypertension are sufficiently complex to defy currently used techniques, and/or nongenetic factors contribute in susceptible individuals.

A favored hypothesis proposed by Brenner [7] is that hypertension may result from a congenital reduction in nephron number. Barker and others have identified a strong relationship between intrauterine growth retardation (IUGR) and low birth weight with the later development of hypertension in the adult [8, 9]. IUGR and low birth weight correlate with impaired renal development [10] and reduced nephron number at birth [11, 12]. A recent autopsy study found that subjects with essential hypertension had nearly 50% fewer nephrons than control subjects [13]. A reduced nephron number results in compensatory hyperfiltration, which may lead to progressive nephron loss over time [14], decreasing ultrafiltration surface area, and limiting sodium excretion [15]. While reduced nephron number will decrease filtered sodium load, few kidney transplant donors develop hypertension, even after many years of follow-up [16], challenging this pathway as a major pathogenic mechanism.

Any proposal for the development of essential hypertension must also take into account the nearly universal presence of arteriolosclerosis and tubulointerstitial inflammation within the kidneys of hypertensive subjects [17, 18]. While many have proposed that these changes

result from hypertension, there is some accruing evidence that the lesions precede the development of hypertension [19]. Goldblatt has even suggested that primary development of the arteriolosclerosis was the cause of hypertension, and that the mechanism involved the induction of renal ischemia [20]. While this hypothesis had been largely discarded, recent studies provide evidence in support of this pathway [21].

In this paper, we present the hypothesis, with preliminary evidence, that an elevation in uric acid may have a key role in the pathogenesis of essential hypertension, and we also present evidence that it may be a factor for the presence of a lower nephron number in subjects with essential hypertension.

HYPERURICEMIA AS A MECHANISM FOR ESSENTIAL HYPERTENSION

Epidemiologic evidence

An elevation in serum uric acid has consistently been found to predict the development of hypertension [22–24]. Population studies have also shown that the frequency of hypertension increases in a continuous and graded fashion with increasing quartile of serum uric acid [25]. The strongest association of uric acid with hypertension is with new onset essential hypertension [26]. In a recent study of adolescents with hypertension, a serum uric acid of >5.5 mg/dL was observed in 89% of essential hypertensive subjects ($N = 63$), in 30% of those with secondary hypertension ($N = 40$), and in 0% of control subjects ($N = 40$) or "white coat" hypertensives ($N = 22$) [26]. The correlation of uric acid with systolic blood pressure in control subjects and subjects with primary hypertension was continuous and strong ($r = 0.8$, $P < 0.001$), and not explained by obesity or decreased renal function [26]. Interestingly, the association between hypertension and serum uric acid is less strong in adults. In the Framingham data, it attenuates with subsequent examinations [27, 28]. This suggests that an elevation in uric acid may be more important in the development of hypertension rather than in its maintenance.

Experimental evidence in animals

The most direct evidence in support of uric acid as a cause of hypertension is the observation that rats made mildly hyperuricemic develop the clinical syndrome of essential hypertension, in which they manifest hypertension, renal arteriolar disease, renal vasoconstriction, with minimal reduction in renal function [29–35]. Prevention of hyperuricemia with allopurinol (a xanthine oxidase inhibitor) or with benziodarone (a uricosuric) also prevented the development of hypertension.
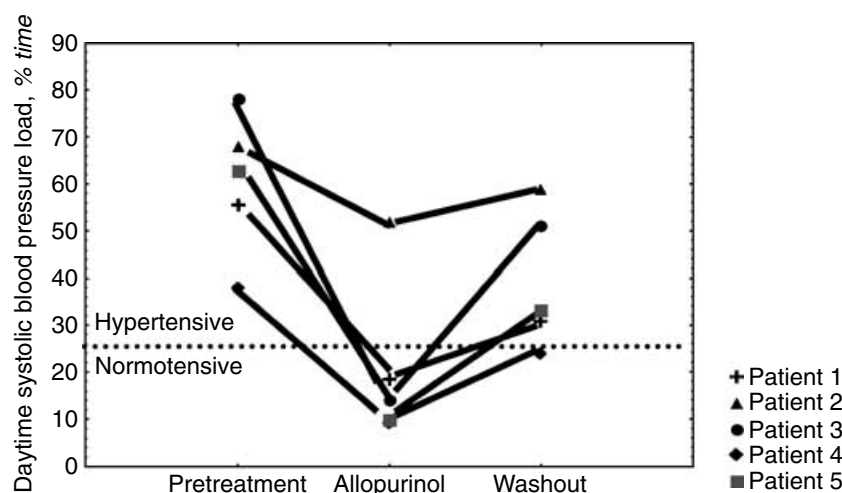
The hypertension in this model was driven by two major mechanisms. The initial hypertension was evident particularly under low-salt dietary conditions, and was associated with an impairment in plasma nitric oxide (NO) concentration [36] and with a reduction in both macula densa nitric oxide synthase-1 (NOS-1) and renal endothelial NOS-3 [29, 37]. Administration of L-arginine (a substrate for NO synthesis) attenuates the increase in blood pressure, confirming the role of decreased NO in the induction of uric acid–mediated hypertension. The increase in blood pressure was also associated with stimulation of juxtaglomerular renin, and could be blocked by an angiotensin-converting enzyme inhibitor or an angiotensin II type I receptor antagonist [29, 30].

Over time, however, the hypertension becomes independent of the serum uric acid levels. The mechanism appears to involve the development of subtle renal microvascular disease [33]. Specifically, hyperuricemic rats developed an arteriolopathy of the afferent arteriole that could be shown to occur independently of blood pressure [30]. The possibility that the arteriolopathy was mediated by a direct action of uric acid is supported by in vitro studies showing that uric acid could induce cell proliferation, as well as the stimulation of cyclooxygenase-2, the local renin angiotensin system, growth factors (platelet-derived growth factor, or PDGF), and chemokines (monocyte chemoattractant protein-1) [33, 35, 38, 39]. After the formation of the arteriolar lesion, the rats developed salt-sensitive hypertension independent of the uric acid level [33]. This is consistent with other animal models in which the development of renal arteriolar disease results in salt-sensitive hypertension. The mechanism for this pathway has been recently reviewed and consists of tubular ischemia with the recruitment of inflammatory cells (T cells and macrophages) that release oxidants and angiotensin II, which cause cortical vasoconstriction and sodium retention [40–44]. Blockade of the vascular and inflammatory processes can ameliorate the hypertension [21, 39–44].

Experimental evidence in man

Proof that uric acid may be involved in the pathogenesis of hypertension in man must await studies examining the effect of lowering uric acid on blood pressure. Because the experimental studies suggest that lowering uric acid will be most likely to show an effect on blood pressure before the development of significant renal microvascular disease, we initiated an open-label pilot study in which adolescents with newly diagnosed essential hypertension were treated with allopurinol for one month followed by a 4-week washout period. As shown in Figure 1, reduction of serum uric acid level from a mean of 6.9 mg/dL to 3.3 mg/dL with 200 mg of allopurinol twice daily significantly reduced casual blood pressure

Fig. 1. Allopurinol lowers uric acid and blood pressure in adolescents with essential hypertension. Children were recruited from the Hypertension program at Texas Children's Hospital. The 5 children had confirmation of their hypertension by in-clinic, home, and ABP monitoring, and were diagnosed with essential hypertension as previously described. Inclusion criteria were newly diagnosed essential hypertension, no current or previous antihypertensive medications or diuretics, serum uric acid >6.0mg/dL, and normal renal function (Schwartz calculation >90cc/min/1.73m^2). Subjects were treated with allopurinol at 200 mg bid for 4 weeks followed by a 6-week washout period off medications. No other interventions, such as exercise or dietary modifications, were made. Casual and ABPM measurements were performed immediately before treatment, at the end of 4 weeks of treatment while still on allopurinol, and 6 weeks after discontinuing the allopurinol. Serum uric acid was measured at the 3 BP measurement visits, as well as one week after the initiation of allopurinol to confirm a >40% decrease in serum uric acid levels. Numbers in parentheses are *P* values, calculated by paired *t* test, in comparison to pretreatment data. The study was open label, and compliance was assessed uric acid levels. No adverse events occurred during the trial. The study was approved by the Baylor Institutional Review Board.

	Pretreatment	Allopurinol	Washout
Uric acid (mg/dL)	6.9 ± 0.6	3.3 ± 0.4 (0.0005)	5.9 ± 0.2 (0.02)
SBP (mm Hg)	140 ± 3.6	131.2 ± 6.1 (0.017)	137.8 ± 5.5 (NS)
DBP (mm Hg)	77.0 ± 8.3	72.8 ± 7.5 (NS)	76.8 ± 7.2 (NS)
SBP load (%)	60.5 ± 14.9	20.7 ± 17.9 (0.009)	39.7 ± 14.7 (0.02)

measurements, and led to normalization of blood pressure by ambulatory blood pressure monitoring (ABPM) criteria in 4 of 5 subjects. One must be careful in the interpretation of the pilot study because of a potential placebo effect; nevertheless, the initial results provide a strong rationale for a future placebo-controlled study.

The above studies support the hypothesis that an elevation in uric acid may have a major role in the pathogenesis of hypertension. Specifically, the studies suggest that uric acid causes endothelial dysfunction, vascular disease, and a 'salt-resistant' hypertension, which then progresses to a renal-dependent pathway of salt-sensitive hypertension. This provides a rationale to perform studies to determine whether lowering uric acid can either prevent hypertension or treat early hypertension.

The relationship of serum uric acid and a congenital reduction in nephron number

An important question is how to converge the uric acid hypothesis with the extensive studies linking congenital reduction in nephron number with the risk for future hypertension. To evaluate this further, we first evaluated the relationship of birth weight with the later development of hypertension in a retrospective chart review of patients enrolled in the Hypertension Program at Texas Children's Hospital. Patients with primary hypertension were distinguished from secondary hypertension, white coat hypertension, and control subjects by extensive workup [26].

As shown in Figure 2A, we found that subjects with primary hypertension had lower birth weights compared with control subjects and subjects with secondary or white coat hypertension. This is consistent with the Brenner hypothesis and suggests that the congenital reduction in nephron number is specific for primary hypertension, as opposed to secondary causes. We also examined the relationship of birth weight with the degree of serum uric acid at presentation. As shown in Figure 2B, we found that the lower the birth weight, the higher the serum uric acid ($r = 0.42$, $P = .0008$). This shows that a low birth weight predicts the serum uric acid in adolescence, and suggests a causal relationship. In this regard, micropuncture studies in uninephrectomized rats show that a reduction in nephron number will result in an increase in absolute proximal reabsorption [45]; because uric acid reabsorption is linked to proximal sodium reabsorption, this might provide a mechanism for the development of hyperuricemia. But then, what causes the congenital reduction in nephron number?

Barker has suggested that maternal factors passed to the fetus during pregnancy may be responsible for the later development of hypertension [8]. Indeed, the familial predisposition toward essential hypertension is stronger if the mother has hypertension in most [46–48], but not all [49], studies. This was also evident in the cohort we studied, in which a history of hypertension in the mother was twice as common as a history of hypertension in the father (Table 1).
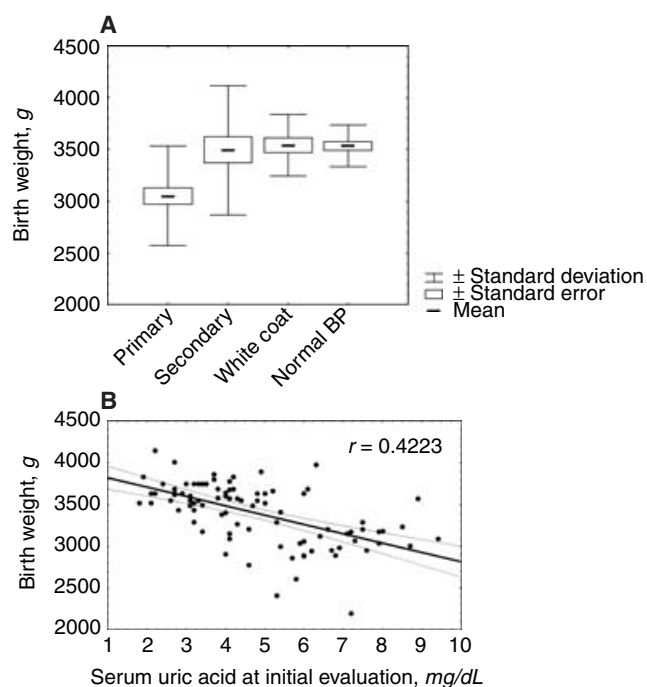
Fig. 2. Serum uric acid in adolescents with essential hypertension correlates inversely with the birth weight of the individual. In a retrospective chart review, the charts of patients enrolled in the Hypertension Program at Texas Children's Hospital were screened for birth weight. Ninety-five children were identified who had recorded birth weight, serum uric acid, and confirmed diagnosis of hypertension (diagnostic protocol described previously). The mean, standard error, and standard deviation of patient's birth weights as a function of their diagnosis are shown (*A*). The correlation analysis for birth weight and serum uric acid at the time of diagnosis of hypertension is shown (*B*).

Table 1. Family history of hypertension in adolescents diagnosed with hypertension in the Texas Children's Hospital Hypertension Program

	Primary $N = 75$	Secondary $N = 63$	White coat $N = 33$	Control $N = 45$
Mother	41.3%	26.9%	27.3%	11.1%
Father	22.7%	12.7%	36.4%	22.2%
Both parents	22.7%	17.4%	6.1%	8.9%
Neither	13.3%	42.8%	30.3%	57.8%

We would like to propose that the 'maternal factor' that causes a reduction in nephron number is a factor that inhibits endothelial cell proliferation, and that one of the principal mediators may be uric acid. Support for this hypothesis is provided by several lines of argument. First, it is known that glomerular development in newborn rats (which continues into the neonatal period) can be inhibited by the administration of anti-vascular endothelial growth factor (VEGF) antibody, a potent inhibitor of endothelial cell proliferation [50]. The susceptibility of the nephrons to inhibitors of endothelial cell proliferation, as opposed to other organs late in pregnancy, may relate to the relative uniqueness of nephron
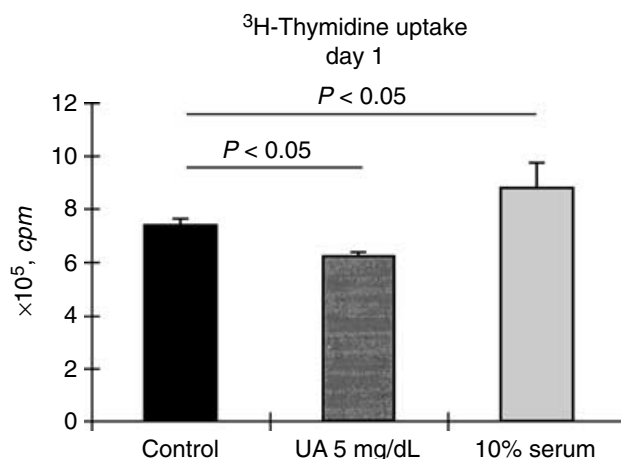

Fig. 3. Inhibition of glomerular endothelial cells by uric acid. Rat glomerular endothelial cells (passage 15, gift of Dr. Stephen Adler, Valhalla, NY) were growth arrested for 24 hours by serum starvation [in Dulbecco's modified Eagle's medium (DMEM) with 0.5% fetal bovine serum (FBS)] on 6-well plates. Cells were then incubated in DMEM (0.5% FBS) with or without uric acid (5 mg/dL) for 24 hours. ^{3}H-thymidine (1 μCi/mL) was added to the culture plates 6 hours before harvest to quantify the glomerular endothelial cell proliferation. Thymidine uptake was assayed by liquid scintillation counting. Studies were performed in triplicate and the cells were all incubated at uniform conditions of 37°C, with 5% CO_2. Comparison was by ANOVA with Bonferroni correction. Physiologic levels of uric acid can significantly inhibit the proliferation of glomerular endothelial cells, a step required for nephronogenesis during late pregnancy, consistent with the possibility that maternal elevations in serum uric acid could contribute to reduced nephron number in the fetus.

development, which is known to primarily occur in the third trimester [11]. Second, uric acid becomes a candidate to block nephron development because it potently inhibits human umbilical vein endothelial cell proliferation in vitro [51]. We have also found that soluble uric acid blocks rat glomerular endothelial cell proliferation under low serum conditions (Fig. 3). Nitric oxide (NO) is also a trophic factor for endothelial cells, and uric acid is an inhibitor of NO production in vitro [51], in animals [36], and in man [52]. Indeed, studies in humans also have found that uric acid levels correlate inversely with plasma NO and with acetylcholine-dependent vasodilation [53, 54], and blockade of uric acid production with allopurinol also improves endothelial-dependent vasodilation in patients with congestive heart failure or diabetes [55, 56]. Third, uric acid is a small substance that is known to freely pass into the fetal circulation, where it has been shown to correlate with the development of IUGR and low birth weight [57].

Perhaps the best evidence is provided by studies in preeclampsia. This is a condition characterized by a marked rise in serum uric acid in the mother during the third trimester, elevated levels of uric acid in the fetus, and a high frequency of IUGR and low birth weights. Not surprisingly, children of preeclamptic mothers have

an increased frequency for the later development of hypertension [58, 59]. The rise in uric acid that occurs in the third trimester in preeclampsia corresponds well with the period when nephron development is impaired in low-birth-weight infants [10]. Higher uric acid levels in preeclamptic mothers correlate more closely with worse fetal outcome than maternal blood pressure [60, 61], and the uric acid level in the fetal cord blood in preeclamptic and control infants has been found to inversely correlate with the birth weight [57]. It was also recently reported that women with gestational hypertension and hyperuricemia without proteinuria have evidence of endothelial dysfunction and deliver growth-retarded babies [62, 63].

Endothelial dysfunction as a general mechanism linking low nephron number to hypertension

The above studies have focused on the role of uric acid as a mediator of endothelial dysfunction, low nephron number, and the development of hypertension; however, it is likely that other mediators may also play an important role. For example, in preeclampsia, a major factor that is present in the circulation is sFLT-1, which is a circulating inhibitor of VEGF [64]. Recently, strong evidence has been provided that sFLT-1 may be largely responsible for the development of hypertension and renal disease in preeclampsia [64]. Another circulating factor that causes endothelial dysfunction is asymmetric dimethylarginine (ADMA), which blocks NO production. Savvidou et al found that maternal ADMA levels correlated with both defective endothelial-dependent vasodilation in the mother and with low birth weights in preeclampsia [65]. Endothelial dysfunction is also common in essential hypertension [66]. Furthermore, early essential hypertension is highly associated with an elevated uric acid level [26], as well as elevated levels of sFLT-1 [67] and ADMA [68]. These studies thus suggest that factors that impair endothelial function might account for both the presence of a low nephron number, as well as possibly directly leading to the development of hypertension. In this regard, we have reported that the administration of an NO synthase inhibitor to rats will lead to the development of an afferent arteriolopathy and tubulointerstitial inflammation that results in persistent salt-sensitive hypertension [42]. Hence, a factor such as uric acid, which causes both endothelial dysfunction and vascular smooth muscle cell proliferation, would be expected to cause the renal lesion that would result in the development of hypertension.

We propose a general pathway linking uric acid to the development of hypertension (Fig. 4). First, we suggest that an elevated uric acid in the mother, particularly during the third trimester, may cross into the placenta along with other substances that may interfere with endothelial dysfunction to cause IUGR and impair nephron development. The increase in maternal uric acid could be caused by the development of gestational hypertension (such as
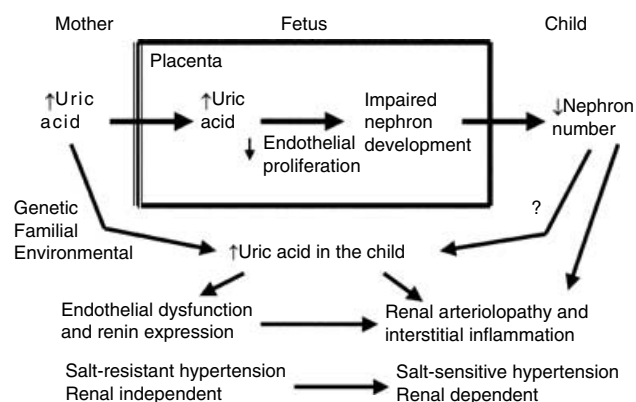

Fig. 4. Hypothetical mechanism by which hyperuricemia leads to reduced nephron number and hypertension. Elevated maternal serum uric acid levels (or other inhibitors of endothelial cell proliferation) cross the placenta into the developing fetus during nephron development. Increases in fetal uric acid levels during the third trimester inhibit endothelial proliferation, a necessary step of nephron development, and reduce the final nephron number at birth. The lower congenital nephron number may lead to hyperuricemia during adolescence as a consequence of increased proximal reabsorption, and hyperuricemia may also result from genetic and environmental factors linked to maternal hyperuricemia. The hyperuricemia causes endothelial dysfunction and hyper-reninemia, which induces a salt-resistant hypertension. The combination of hyperuricemia with the hemodynamic consequences of low nephron number leads to subtle renal injury (arteriolopathy and interstitial inflammation) and the development of a renal-dependent, salt-sensitive hypertension that eventually becomes independent of serum uric acid levels.

related to pre-existing hypertension, obesity, or renal dysfunction, all conditions associated with higher uric acid levels in the nonpregnant patient) or from the development of preeclampsia. Once born, the child will have a decreased nephron number, with relative hyperfiltration occurring in his/her glomeruli. It remains possible that the low nephron number might itself predispose to the development of hyperuricemia as a consequence of an increase in proximal tubular reabsorption [69], which might stimulate uric acid reabsorption (which is linked to sodium reabsorption in the proximal tubule). It also seems likely that an elevation of uric acid in the child could occur from genetic, familial, or environmental (such as diet shared by mother and child) mechanisms, for as mentioned, the mothers of these children frequently themselves manifest underlying hyperuricemia, obesity, and/or hypertension. Thus, these children would be expected to have evidence for higher serum uric acid levels and/or evidence of endothelial dysfunction during childhood and before their development of hypertension. Consistent with this hypothesis, children with low birth weights do have evidence for both impaired endothelial cell vasodilation (at age 9 to 11) [46] and decreased capillary recruitment [47]. Subjects at risk for developing essential hypertension are also more likely to have impaired microvascular dilation and increased capillary rarefaction [70], and an increased serum uric acid [22, 23]. Eventually, the combination of the low nephron number, coupled with the concurrent

endothelial dysfunction, leads to the development of initially a salt-resistant hypertension (driven by endothelial dysfunction and renin activation), followed by a salt-sensitive hypertension (driven by kidney ischemia mediated by the arteriolopathy and interstitial inflammation). Indeed, there is evidence that the presence of a low nephron number and hyperuricemia are additive in their ability to induce renal injury [71], and both conditions also independently result in glomerular hypertension [14, 31]. It is also possible that a marked increase in serum uric acid could induce hypertension independently of nephron number, as suggested by the experimental studies in animals [29, 30].

The presence of maternal factors that inhibit endothelial and glomerular development could also explain two confusing observations regarding essential hypertension. Keller et al [13] observed that men with essential hypertension have fewer nephrons; however, renal transplant donors who also have reduced nephron mass do not develop hypertension more frequently than the population at large [16]. If the cause of congenital reduction in nephron number is a diffusible inhibitor of nephron development acting through altered endothelial and vascular smooth muscle function, transplant donor nephrectomy would not be expected to cause the same results. Second, maternal factors that modify genetically conferred risk would not be detectable on genetic linkage analysis or microarray expression analysis, and would in part explain the difficulties in establishing the genetic basis for essential hypertension.

CONCLUSION

We present a hypothesis linking endothelial dysfunction, driven by an elevated uric acid and other substances, to cause the congenital reduction in nephron number that is associated with the later development of hypertension. We also suggest that an elevation in uric acid may be a critical initiator of the renal mechanisms leading to the development of essential hypertension via both its ability to cause endothelial dysfunction and renin activation, and by causing intrarenal lesions that mediate the development of salt-sensitivity. Further studies are necessary to prove different aspects of this pathway.

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