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RESEARCH ARTICLE

Relationship between serum uric acid levels and arterial blood pressure in Egyptian young males

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Abstract

Background: Hyperuricemia is an independent risk factor for hypertension, and uric acid has pro-oxidant and pro-inflammatory effects. Adolescents with high serum uric acid levels may be at risk to develop hypertension, cardiovascular or renal disease later in their life. A correlation between uric acid in childhood and blood pressure was found in all race and sex groups except black males. Lowering serum uric acid should be made as early as possible, as once intrarenal vascular changes occur, hypertension becomes more related to renal disease than uric acid. The aim of this work was to study the relationship between serum uric acid levels and arterial blood pressure in Egyptian young males, without hypertension or other medical diseases.

Subjects and methods: This study was carried out on 950 Egyptian young males, (20-30) years old, for whom blood pressure was measured, and then 200 subjects were selected, after excluding hypertension, hypotension, diabetes mellitus, renal disease, clinical gout and cigarette smoking. Repeated blood pressure measurements were made, and the average systolic, diastolic and mean blood pressures were calculated, in addition to weight, height and waist circumference. Laboratory investigations including serum uric acid, fasting blood glucose, renal function tests, and urine analysis had been made for them.

Results: Serum uric acid levels were divided into quartiles; 1st quartile (3.1-4.2 mg/dl), 2nd quartile (4.3-4.8 mg/dl), 3rd quartile (4.9-5.4 mg/dl) and 4th quartile (5.5-6 mg/dl). We found that systolic, diastolic and mean blood pressures in subjects with serum uric acid levels in the 4th quartile (130.14±4.73, 86.31±1.09 and 100.92 ± 2.45 mmHg), were significantly higher than those in the 3rd quartile (122.59±3.77, 82.54±1.80 and 95.89 ± 1.97 mm Hg), than those in the 2nd quartile (115.26±2.99, 77.67±1.6 and 90.2 ± 1.97 mm Hg), than those in the 1st quartile (106.1±3.41, 72.79±1.37 and 84.65 ± 1.55 mm Hg), all P values < .01, while no significant differences were found among the serum uric acid quartiles as regards the age, weight, height, waist circumference, or serum creatinine, all P values > .05. There was a significant positive correlation between each of uric acid, waist circumference and age and each of systolic, diastolic and mean blood pressures; all P values<.05. Serum uric acid levels were found to be independently and positively related to each of systolic, diastolic and mean blood pressures, when waist circumference and age were adjusted; all P values < 0 .01.

Conclusion: Serum uric acid levels are related to arterial blood pressure in Egyptian young males, and subjects with high normal uric acid levels have prehypertension. Reducing serum uric acid levels in such persons might help prevent their developing hypertension.

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Introduction:

Hyperuricemia has been demonstrated to predict and to be an independent risk factor for hypertension in adults **(1).** Earlier studies in children and young adults showed uric acid levels were higher in white subjects and were associated with higher diastolic blood pressure and lean body mass **(2).** Despite similar body mass indices (BMIs) in adulthood, males had significantly higher blood pressure (BP) levels compared with females and blacks compared with whites. A correlation between uric acid in childhood and BP was found in all race and sex groups except black males. The reason for differential effect of serum uric acid on BP between the sexes is unknown but may be at least partially explained by the gender-specific differences in salt sensitivity **(3).** Once elevated uric acid levels cause sufficient renal injury, animals develop salt-sensitive hypertension regardless of the level of uric acid. Thus, maintaining a lower uric acid would be more effective at prevention rather than lowering uric acid in the treatment of hypertension because once intrarenal vascular disease develops, hypertension is then driven by renal disease **(4).** Uric acid can enter vascular smooth muscle cells and stimulate platelet-derived growth factor and mitogen-activated protein kinase. These factors induce vascular smooth muscle proliferation and preglomerular arteriolopathy. The mechanism of the persistent salt sensitivity is thought to be attributable to renal ischemia that leads to activation of the renal renin-angiotensin system, renal vasoconstriction, and increased sodium reabsorption **(5).** Although uric acid has some antioxidant activity, its pro-oxidant effects predominate and are mediated through the urate radical, stimulating the synthesis of pro-inflammatory molecules, or from xanthine oxidase, which generates free radicals in its enzyme activity **(6).** In addition, a study on adolescents found that 90% of primary hypertension was associated with high (>5.5 mg/dl) serum uric acid levels, whereas uric acid was not elevated in secondary hypertension **(7).** Even high-normal values of serum uric acid may reduce renal function, which is in agreement with results from experiments in rats. In rats rendered mildly hyperuricemic by being fed a urate oxidase inhibitor, an afferent arteriolopathy developed and was accompanied in some cases by an increase in BP **(8).** Lowering serum uric acid concentration with allopurinol attenuated these histologic and functional changes, but this effect may in part be due to reduced oxidative stress **(9).** The longitudinal relationship between serum uric acid and systolic blood pressure in non-diabetic adults remained significant after adjusting for age, sex, race and serum creatinine, but dissipated after adjusting for waist circumference and smoking status **(8).** Elevated serum uric acid level is also common in subjects with prehypertension **(7).** A randomized, double-blind, placebo-controlled study compared allopurinol with probenecid, in pre-hypertensive obese adolescents. Both treatment arms had a significant decrease in serum uric acid, and led to a 10.2 and 9.0 mm Hg reduction in systolic and diastolic blood pressure, respectively. These results suggested that reduction in blood pressure was related to the urate lowering effect and not to the decreased xanthine oxidase activity **(10).** Asymptomatic hyperuricemia has a deleterious effect on the progression of chronic kidney disease and the control of hypertension. This effect was blocked by treatment with renin-angiotensin system blockers **(11).** A significant independent association was found between uric acid with both systolic and diastolic blood pressure; an increase in both systolic and diastolic blood pressure was also marked by a corresponding increase in serum uric acid concentration. Subjects with pre-hypertension were averagely younger and had a higher mean serum uric acid concentration than those with hypertension **(12).**

Patients and methods:

This study was conducted on 950 Egyptian young males (20–30) years old, with no history of medical diseases. Ethical formal consent from every subject was obtained after explaining the aim, benefits and the procedure of the work. Blood pressure was measured for all of them, and then 200 subjects were selected to continue the study. Exclusion criteria included cigarette smoking, hypertension, hypotension, diabetes mellitus, renal disease, and clinical gout. After careful history taking, clinical examination, blood and urine samples had been withdrawn, for testing serum uric acid, serum creatinine, fasting blood glucose, and urine analysis. Special measurements had been taken including; weight, height, waist circumference and repeated blood pressure measurements. All measurements were performed in the mobile examination center. After 5 minutes of resting in the sitting position, 3 arm measurements were performed using a cuff size appropriate for the individual. When needed, a fourth measurement was performed. For our analyses, we calculated the average of these measures; average value of systolic, diastolic and mean blood pressure, for each participant. Based on recommendations of the (JNC 7), the classification of BP

for adults has been as follows: Normal: Systolic lower than 120 mm Hg, diastolic lower than 80 mm Hg. Prehypertension: Systolic 120-139 mm Hg, diastolic 80-89 mm Hg. Stage 1: Systolic 140-159 mm Hg, diastolic 90-99 mm Hg. Stage 2: Systolic 160 mm Hg or greater, diastolic 100 mm Hg or greater **(23).**

Results:

Statistical analysis was done using Statistical analysis was done using SPSS version 20 for windows. Data were presented as mean ± SD compare means between groups was done by ANOVA test, followed by Tukey as a post-hoc test. A 2 tailed P value was as follow: P>.05 non significant (NS), P<.05 significant (S), P<.01 highly significant (HS), P<.001 very highly significant (VHS). Correlation between variable was done by Pearson correlation analysis. **Table (1)** shows demographic data of studied participants. **Table (2)** shows a comparative analysis among quartiles of serum uric acid levels. Range of serum uric acid in the 1st quartile was (3.1-4.2 mg/dl), the 2nd quartile (4.3-4.8 mg/dl), the 3rd quartile (4.9-5.4 mg/dl) and the 4th quartile (5.5-6 mg/dl); P1 between 1st & 2nd quartiles, P2 between 2nd & 3rd quartiles, P3 between 3rd & 4th quartiles and P overall. Values of systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean blood pressure (MBP) were significantly higher in the 4th quartile of serum uric acid levels when compared with values in the 3rd quartile, in 3rd quartile when compared with values in the 2nd quartile, and in the 2nd quartile when compared with values in the 1st quartile, all P values < .01. There was no significant difference between all quartiles of serum uric acid quartiles as regards the age, weight, height, waist circumference (WC) or serum creatinine (Sr Cr); all P values > .05. **Table (3)** shows correlation between systolic, diastolic and mean blood pressure and each of uric acid, waist circumference and age. There was a significant positive correlation between each of serum uric acid levels, WC and age and each of SBP, DBP and MBP; all P values<.05. **Table (4)** shows a multivariate linear regression analysis, using systolic, diastolic and mean blood pressures as dependent variables. Serum uric acid levels were found to be independently and positively related to each of systolic, diastolic and mean blood pressures, when WC and age were adjusted; all P values<0 .01.

Table 1: Demographic Data

Factor	All participants (N=200)	Maximum	Minimum
Age	25.19 ± 1.86	30.5	20
Height	170.09 ± 3.06	195	145
Weight	79.87 ± 1.57	145	52
SBP	117.73 ± 2.86	135	93
DBP	79.35 ± 1.36	91	70
MBP	92.36 ± 2.54	105.67	79
Waist circumference	94.37 ± 2.32	136	90
S. creatinine	1.03 ± 0.2	1.4	0.7
S. uric acid	5.07 ± .41	6	3

Table 2: Comparative analysis among quartiles of serum uric acid levels

Factor	1st quartile	2nd quartile	3rd quartile	4th quartile	P1	P2	P3	P
Age	24.55±2.67	25.35±2.53	25.46±2.19	25.55±2.1	.454	.998	.999	.248
Height	172.3±6.59	171.88±7.81	168.92±8.53	169.8±9.2	.992	.3	.957	.123
Weight	79.6±13.77	78.74±17.28	76.51±13.23	80.08±16.87	.991	.902	.106	.227
SBP	106.1±3.41	115.26±2.99	122.59±3.77	130.14±4.73	< .0001	<.0001	< .0001	< .0001
DBP	72.79±1.37	77.67±1.6	82.54±1.80	86.31±1.09	< .0001	<.0001	< .005	< .0001
MBP	84.65±1.55	90.2 ± 1.97	95.89 ± 1.97	100.92 ±2.45	< .0001	<.0001	<.0001	< .0001
WC	94.36±9.2	92.43±8.91	94.12±8..7	96.73±16.5	.804	.892	.702	.291
Sr Cr	1±.17	1.05±.21	1.05±.2	1.1±.21	.511	1	.759	.406

Table3:Correlation between systolic, diastolic and mean blood pressure and other parameters
r, correlation coefficient

Factor	Systolic blood pressure		Diastolic blood pressure		Mean blood pressure	
	r	P	r	P	r	P
Serum uric acid	.465	<.0001	.326	<.0001	.426	<.0001
Waist circumference	.307	<.0001	.208	.003	.258	.002
Age	.192	.007	.179	.011	.188	.008
Weight	.074	.127	.085	.122	.078	.125
Height	.164	-.114	.086	-.122	.109	-.099

Table 4: Multivariate linear regression analysis using systolic, diastolic and mean BPs as dependent variables.

	Systolic blood pressure		Diastolic blood pressure		Mean blood pressure	
	B	P	B	P	B	P
Serum uric acid	3.196	< .0001	1.66	< .0001	2.28	< .0001
Waist circumference	.280	< .0001	0.135	0.006	.210	.003
Age	.459	.015	.415	.026	.441	.018

B, unstandardized coefficient

Figure 1 Linear regression analysis using systolic blood pressure as a dependent variable

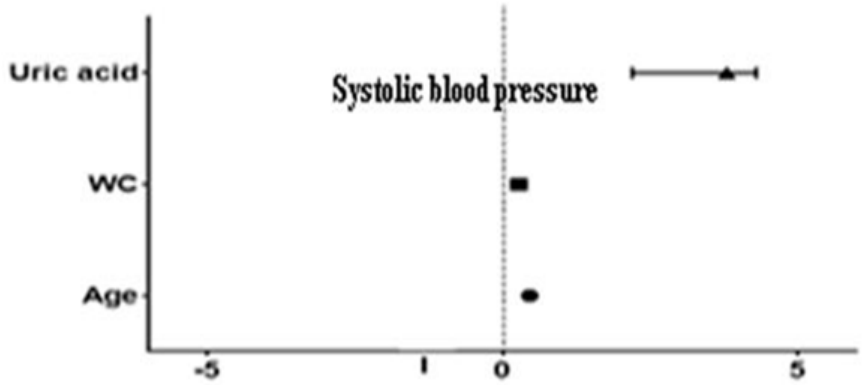


Figure 2 Linear regression analysis using diastolic blood pressure as a dependent variable

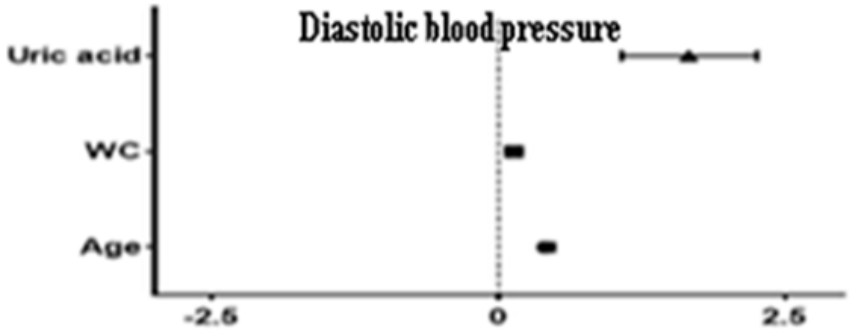
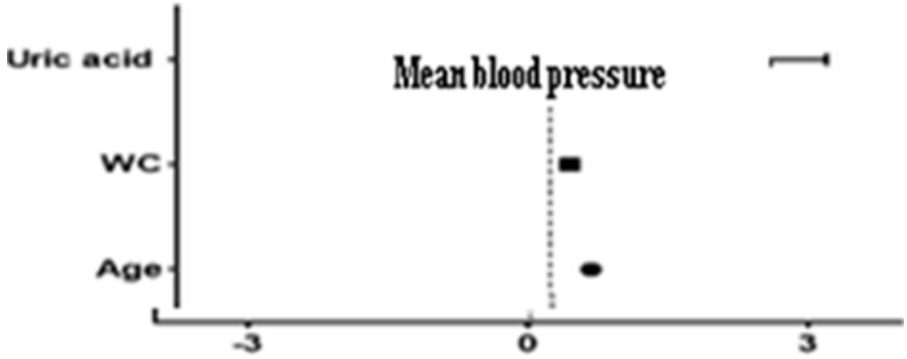


Figure 3 Linear regression analysis using mean blood pressure as a dependent variable



Discussion:

Adolescents are an ideal population in which to examine the relationship between serum uric acid and the development of hypertension, because it has been hypothesized that uric acid may be most significant in the development of early hypertension before significant vascular damage has occurred and may have less influence on blood pressure levels once vascular damage is permanent. In addition, adolescents are less likely to have comorbidities that can make examining this relationship in adults more complex **(13).** This study was carried out on 950 Egyptian young males, for whom blood pressure was measured and then only 200 subjects were selected for the study, after the exclusion of hypertension, hypotension, cigarette smoking, diabetes mellitus, clinical gout or renal disease. In our study, data of the included subjects were divided according to serum uric acid levels, into quartiles as follows: 1st quartile (3.1-4.2 mg/dl), 2nd quartile (4.3-4.8 mg/dl), 3rd quartile (4.9-5.4 mg/dl), and 4th quartile (5.5-6 mg/dl). We found that systolic, diastolic and mean blood pressures in subjects with serum uric acid levels in the 4th quartile (130.14±4.73, 86.31±1.09 and 100.92 ± 2.45 mmHg), were significantly higher than those in the 3rd quartile (122.59±3.77, 82.54±1.80 and 95.89 ± 1.97 mm Hg), than those in the 2nd quartile (115.26±2.99, 77.67±1.6 and 90.2 ± 1.97 mm Hg), than those in the 1st quartile (106.1±3.41, 72.79±1.37 and 84.65 ± 1.55 mm Hg), while no significant differences were found among the serum uric acid quartiles as regards the age, weight, height, waist circumference, or serum creatinine. There was a significant positive correlation between each of uric acid, waist circumference and age and each of systolic, diastolic and mean blood pressures, while no correlation was found between each of weight and height and each of systolic, diastolic and mean blood pressures. Serum uric acid levels were found to be independently and positively related to each of systolic, diastolic and mean blood pressures, when waist circumference and age were adjusted. This is in agreement with **(13),** who found that among US adolescents, participants with elevated blood pressure had a mean uric acid of 5.6 mg/dl compared with 5.0 mg/dl in the normal blood pressure group, and after age, sex, race/ethnicity, and BMI adjustment, the odds ratio of having elevated blood pressure for each 0.1 mg/dl increase in uric acid was 1.38 (95% CI: 1.16 –1.65). In stratified analysis, the odds ratio for elevated blood pressure for each 0.1 mg/dl increase in uric acid was 1.45 (95% CI: 1.17–1.80) in males and 1.17 (95% CI: 0.84 –1.61) in females. As uric acid quintile increased, participants were more likely to be older, male, and white; to have higher weight, height, BMI, and systolic blood pressure percentiles; to be obese; and to have elevated blood pressure. Similarly, another study **(12)** found a significant independent association between uric acid with both systolic and diastolic blood pressure and that an increase in both systolic and diastolic blood pressure was also marked by a corresponding increase in serum uric acid concentration. In our study, although we excluded hypertensive subjects, we found that Egyptian young males (20-30 years), with serum uric acid levels in the 3rd quartile of normal range, had stage 1 prehypertension (120-129/80-84 mmHg), systolic and/or diastolic, and those in the 4th quartile had stage 2 prehypertension (130-139/85-89 mmHg), systolic and/or diastolic. Patients with prehypertension should be treated with life style modifications in stage 1 prehypertension and with angiotensin receptor blockers (ARBs) and/or angiotensin converting enzyme (ACE) inhibitors in stage 2 prehypertension, in addition to life style modifications **(24).** This is in agreement with another study **(14),** who found that higher serum uric acid levels were positively associated with prehypertension, independent of smoking, body mass index (BMI), diabetes, kidney function and other confounders. The multivariable odds ratio [95% confidence intervals] comparing quartile 4 of uric acid (>356.9 umol/l) to quartile 1 (<237.9 umol/l) was 1.96 (1.38-2.79), and this association persisted in separate analysis among men and women. Participants with uric acid level ≥5.5 mg/dL had twice the odds of having elevated blood pressure compared with those with a uric acid level ≥5.5 mg/dL. Compared with the lowest uric acid quintile, participants in the highest quintile had 3-fold higher odds of elevated blood pressure. The

results were similar for the association of uric acid levels with systolic and diastolic blood pressure z scores. Normative values of uric acid are higher in males and may be affected by onset of puberty, body mass differences, and hormonal effects. Significant differences in uric acid levels were noted between male and female adolescents. Males had higher odds than females of having an elevated blood pressure with increasing uric acid level **(13).** Although subjects in our study were young, and most risk factors for hypertension were excluded in them, they showed strong correlation between blood pressure and serum uric acid levels, within the normal range. Should this point to the necessity to re-adjust the cut point at which serum uric acid levels are considered to be normal? Most physicians shall not start therapy to reduce serum uric acid levels that are still within the normal range. Waiting till patients develop hypertension or have higher than normal serum levels of uric acid, means that the inflammatory effect of uric acid and the complications of the prehypertension shall be left untreated, although this can be prevented by simply using allopurinol or other measures to reduce serum uric acid levels. If that is the case in young males, this should be of greater importance, when it comes to older subjects, and those with additional risk factors for hypertension and vascular diseases. Starting allopurinol early, while serum uric acid levels are still normal, should be tested, as well. Uric acid has been suggested to play a role in the pathogenesis of early onset hypertension, in addition to the risk of hypertension in the elderly **(15).** A significant negative correlation was found between uric acid and age; those with prehypertension who were averagely younger had a higher mean uric acid concentration than hypertensive participants **(12).** Serum uric acid levels may tend to dampen with age where stiffening of the aorta, activation of the renin-angiostensin system and renal vasoconstriction may have a role to play **(16).** A clinical trial of 30 adolescents **(7),** with newly diagnosed primary hypertension and uric acid levels ≥6 mg/dL treated with 400 mg/d of allopurinol versus placebo for 4 weeks. This trial demonstrated a mean change in casual systolic blood pressure of ≥6.9 mmHg during allopurinol treatment compared with ≥2.0 mmHg during placebo, and a mean change in 24-hour ambulatory systolic blood pressure of ≥6.3 mmHg for allopurinol and ≥0.8 mmHg for placebo. Allopurinol is known to have an anti-inflammatory effect by itself, which might be claimed to be the reason of lowering blood pressure after its use, apart from the effect of serum uric acid level lowering. Our results showed that serum uric acid levels are related to blood pressure, as our patients were not given allopurinol. Another possibility could be that blood pressure itself might be affecting serum uric acid levels. If this is true, it means that reducing blood pressure and treating prehypertension might prevent hyperuricemia or gout. Allopurinol is also used sometimes in treating patients with hypertension, which might be explained by its direct effect as a xanthine oxidase inhibitor, on serum uric acid levels and as an anti-inflammatory and antihypertensive. Future studies should compare the effects of reducing serum uric acid through using allopurinol to the use of dietary restriction and other measures, to detect if their effect on blood pressure is related to serum uric acid or inflammation or both. Elevated serum uric acid levels have been associated with hypertension in large epidemiological studies in adults. Controversy remains as to whether uric acid is an independent causal factor, a mediator, or merely a marker for the development of hypertension **(17).** In our study, blood pressure was also found to be correlated to the age, and waist circumference, in addition to serum uric acid. The adjustment of age and waist circumference did not significantly change the effect of serum uric acid on the blood pressure. This means that serum uric acid levels might have greater impact as a risk factor in the development of hypertension than obesity or aging. In addition, each of systolic, diastolic and mean blood pressures was positively and significantly correlated to each serum uric acid, waist circumference and age, but this relation between blood pressure and serum uric acid continued even after the adjustment of waist circumference and age. Also, as no significant difference was found as regards the age, weight or waist circumference among the four quartiles of serum uric acid levels, while a significant difference was found as regards systolic, diastolic and mean blood pressures, we can explain that serum uric acid levels have strong relation on blood pressure by itself. This is in agreement with **(13),** who found that inclusion of diabetes mellitus, hyperlipidemia, tobacco exposure, and annual household income in logistic and linear regression analyses did not change the relationship of uric acid with blood pressure. Hyperuricemia is commonly associated with metabolic syndrome **(18)**, and has been implicated in hypertension through the probable role it is thought to play in mediating hypertension via mechanisms like inflammation, vascular smooth muscle cell proliferation in renal microcirculation, endothelial dysfunction and activation of the rennin – angiotensin – aldosterone system **(19).** It is well established that when uric acid is deposited in tissues in the crystalline form, it initiates a pro-inflammatory state, as seen in gouty arthritis and hyperuricemia is associated with elevated CRP and other inflammatory markers in a cohort of elders **(20).** In our study, we did not measure markers of inflammation which should be considered in future studies to study the relation between serum uric acid levels and markers of inflammation and their impact on blood pressure in young adults. Talaat and Elsheikh **(11)** found that asymptomatic hyperuricemia has a deleterious effect on the progression of chronic kidney disease and the control of hypertension. This effect was clear in patients who stopped allopurinol, and was blocked by treatment with renin-angiotensin system blockers. Uric acid also behaves as a pro-oxidant and pro-inflammatory factor. While being a potent antioxidant in extracellular fluid, uric acid exerts pro-oxidative

effects once inside the cell **(21).** Because uric acid is said to have an antioxidant effect, lowering its levels below normal range might have adverse effects. Using allopurinol or other medications to lower serum uric acid in patients with prehypertension, hypertension or other cardiovascular risk factors could be limited also by its side effects and drug interactions. There are no universally accepted clinical recommendations for the management of mild and moderate asymptomatic hyperuricemia in patients with chronic kidney disease apart from dietary protein and purine restriction **(22).** In our study the effect of serum uric acid was noticed on both systolic and diastolic blood pressure. This requires further studies, to detect the exact mechanisms, affecting both systolic and diastolic blood pressure, as regards the serum uric acid levels. Another point should be evaluated as regards to the effect of diet on both serum uric acid and blood pressure. In other words, could there be certain type of food or drink that can affect both blood pressure levels? This could help prevent and treat both conditions through diet. Further studies should be carried out, on adolescents and young adults, to study markers of inflammation and correlate them with serum uric acid and hypertension, and their response to medications used to reduce serum uric acid. The requirement to reduce the normal range for serum uric acid, above which treatment is started, should also be evaluated. Comparison between the effects of reducing serum uric acid using non pharmacological measures versus the use of medications should be studied as well, to detect whether the reduction of blood pressure is related to the reduction of serum uric acid itself or to the anti-inflammatory effect of allopurinol. Follow up of young males with high normal serum uric acid levels and prehypertension should be studied to detect their possible development of hypertension, renal or cardiovascular complications.

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