Uric Acid and Endothelial Dysfunction in Essential Hypertension

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Abstract

Background: Uric acid (UA) can stimulate the biosynthesis of c-reactive protein (CRP), and that might be one of the mechanisms underlying the endothelial dysfunction. Several studies showed an independent link between UA and CRP suggest that chronic exposure to mild hyperuricemia may be a factor that contributes to micro inflammation and raised CRP in individuals with essential hypertension.

Aim: The aim of this study is to investigate the relationship between the serum uric acid, CRP , total cholesterol and endothelial dysfunction in patient with essential hypertension .

Patients and methods: Twenty patients with essential hypertension and fifteen apparently subjects matched for age and weight have been included in this study, Uric acid and total cholesterol were determined by enzymatic methods. High sensitivity C-reactive protein (HsCRP) enzyme immunoassay for the quantitative determination in human serum was used.

Results: The data obtained showed that the serum levels of uric acid, CRP and total cholesterol were significantly higher in patients with hypertension than in healthy controls.

Conclusion: The conclusion was that hyperuricemia in individuals with essential hypertension is associated with endothelial dysfunction. This association, which is independent of classical risk factors like total cholesterol, CRP, supports the hypothesis that UA plays a significant role in this alteration in humans.

الخلاصة

الخلفية: إن حامض اليوريك يمكن أن يحفّز تأليف البروتين التفاعلي سي، وقد تكون تلك أحد الآليات التي تقع تحت عطل endothelial . أظهرت عدّة دراسات بوجود علاقة بين حامض اليوريك و البروتين التفاعلي سي حيث أظهرت تلك الدراسات بان التعرّض المزمن إلى hyperuricemia قد يكون العامل الفعال الذي يساهم في الالتهاب الدقيق ورفع تركيز البروتين التفاعلي سي في الأشخاص المصابين بارتفاع ضغط الدم.

إنّ هدف هذه الدراسة هو التحرّى عن العلاقة بين حامض اليوريك، اليروتين التفاعلي سي، الكولوستيرول الكليّ وعطل endothelial في المرضى المصابين بارتفاع ضغط الدم .

المرضى والطرق: تضمنت الدراسة اختيار عشرون مريض مصاب بارتفاع ضغط الدم (12 من الذكور و 8 إناث) تراوحت أعمارهم مابين 40-60 سنة وخمسة عشر حالة من الاصحاء (8 من الذكور و 7 من الاناث) ولنفس الأعمار . وقد تم قياس حامض اليوريك والكولوستيرول الكليّ وكذلك تم قياس البروتين التفاعلي سي عالي الحساسية (HsCRP) وبواسطة الطريقة المناعية immunoassay.

النتائج: اظهرت الدراسة بان هناك زيادة معنوية في مستويات مصل حامض اليوريك، البروتين التفاعلي سي والكولوستيرول الكليّ في المرضى المصابين بإرتفاع ضغط الدم بالمقارنة مع الأصحاء .

الخاتمة: اقترحت الدراسة بان زيادة الحامض البولي مع ارتفاع ضغط الدم والذي يؤدي الى عطل endothelial وهذا الارتباط لا علاقة له من الخطر الكلاسيكي من وجود الكولسترول الكلي والبروتين التفاعلي سي ويلعب حامض اليوريك دور كبير في هذا التعديل في الإنسان.

Introduction

The association of hyperuricemia with hypertension has long been recognized [1]. It remains unresolved whether the association of hyperuricemia with hypertension is solely because of underlying renal and metabolic abnormalities. Extensive epidemiologic and experimental evidence now suggests that serum uric acid (UA) is a relevant and

independent risk factor for cardiovascular and renal disease, particularly in patients with hypertension, heart failure, or diabetes. Hyperuricemia predicts mortality in patients with heart failure or coronary heart disease [(2)], cerebrovascular events in individuals with diabetes and cardiac ischemia in hypertension .The mechanism(s) by which UA may engender organ damage is still incompletely understood, but there is increasing evidence that endothelial dysfunction is a fundamental mechanism whereby this substance may affect cardiovascular and renal function and structure [(3)]. The relationship between UA levels and endothelial dysfunction has been explored only in a study that combined seemingly healthy individuals and patients with preexisting cardiovascular diseases of various severity or in individuals at increased cardiovascular risk [(4)]. Essential hypertension is consistently associated with endothelial dysfunction ,and hyperuricemia is a strong predictor of hypertension and BP progression [(5)]. Therefore, individuals with essential hypertension constitute an interesting population in which to investigate the relationship between UA and endothelial dysfunction. It is noteworthy to mention that focusing on a drug-free population without cardiovascular complications seems important because these factors are notorious confounders in the interpretation of hemodynamic tests of endothelial function [(6)]. UA can stimulate the synthesis of CRP, and that might be one of the mechanisms underlying the endothelial dysfunction. Several studies showed an independent link between UA and CRP suggest that chronic exposure to mild hyperuricemia may be a factor that contributes to micro inflammation and raised CRP individuals with essential hypertension. [(7)].

The aim of this study is to investigate the relationship between the serum uric acid, CRP, total cholesterol and endothelial dysfunction in patient with essential hypertension

Subjects and methods

This study has included twenty essential hypertensive patients (12 male and 8 female) with age ranged between 40-60 years and fifteen (8 male and 7 female) apparently subjects matched for age and weight have been studied, attending the out patients consultation clinic of Baghdad teaching hospital in medical city, in a period from October 2009 to March 2010.

- All patients underwent a clinical examination to exclude the presence of secondary hypertension
- Essential hypertension was defined as a diastolic blood pressure ≥ 90 mmHg, systolic blood pressure ≥ 140 mmHg, or self- reported use of antihypertensive medication
-Blood was taken from antecubital vein with the patient in the recumbent position after an overnight fast

-Total cholesterol was determined by enzymatic methods as its one of the metabolic risk factors of hypertension [(8)]. Uric acid was determined using enzymatic methods based on the measurement of Jaffe chromogen and by the URICASE/ POD (Boehringer Mannheim, Mannheim, Germany) method implemented in an autoanalyzer , high sensitivity C-reactive protein (HsCRP) enzyme immunoassay for the quantitative determination in human serum was used. DRG international. Inc. USA. Which is done by ELASA test. [(9)].

Statistical Analyses

Descriptive statistics for all data of each set were expressed as mean ± S.D, and the percent of abnormal value in any test was calculated as above or below the mean ± S.D of the normal values for the matched control group, were compared using independent sample (t) test $P< 0.005$ were considered statistically significant .

The overall predictive values for the results in the studied groups were performed according to program of office xp.

Results

Results obtained in the present study showed that the serum levels of uric acid, C-Reactive protein and total cholesterol were significantly higher in patients with Hypertension than in healthy controls. are shown in table (1).

Table 1. Mean ±SD of serum uric acid, CRP and total cholesterol in patients and healthy controls.

Type	Patients (n=20) Mean □SD	control (n=15) Mean □SD
Uric acid(mg/dl)	8.03± 3.50	4.32±1.07
C-Reactive protein (mg/dl)	5.6 ±1.69	3.8 ±1.15
Total Cholesterol (mg/dl)	138.4 ± 9.4	164 ±53.4

Discussion

This study shows that serum UA concentration in individuals with uncomplicated, untreated essential hypertension is associated with endothelial dysfunction independent of traditional and emerging risk factors.

Endothelial dysfunction, commonly observed in cardiovascular and renal diseases, is attributed to oxidative stress, dyslipidemia (elevated total cholesterol level in the blood), accumulation of endogenous inhibitors of NO synthase, genetic factors, and other causes [9]. Few studies were conducted in humans and available data are controversial. In patients with heart failure [10], with type 2 diabetes [11], at increased cardiovascular risk [10], and with hypercholesterolemia but not in patients with essential hypertension [12], allopurinol, a xanthine oxidase inhibitor that lowers UA and interacts with anion superoxide generation [13], improves endothelial dysfunction. In the study of Mercuro et al. [14], the beneficial effect of allopurinol could have been a direct consequence of the reduced UA levels rather than of superoxide anions mediated by xanthine oxidase inhibition because of the close correlation found between the amount of that decrease and the improvement of endothelial function

High UA levels have been associated with organ damage in hypertensive patients and are considered an integral part of the biochemical alterations that compound the metabolic syndrome. Indeed, serum UA is higher in hypertensive patients with target organ damage [15], as well as in seemingly healthy men [16].

These data suggest that chronic exposure to mild hyperuricemia is a factor that contributes to endothelial dysfunction in patients with uncomplicated, untreated primary hypertension. Inflammation may be a relevant pathway in cardiovascular damage caused by UA [17]. The hypothesis that UA may act as a proinflammatory agent is supported by observations of patients with heart failure [18] and more recently in an elegant experimental study [17]. These data demonstrate that UA can stimulate the synthesis of CRP, and that might be one of the mechanisms underlying the endothelial dysfunction. These data are showing an independent link between UA and CRP suggest that chronic exposure to mild hyperuricemia may be a factor that contributes to microinflammation and raised CRP in individuals with essential hypertension. In this regard, it is important to note that in this and in a previous study [19]. The observation that the UA–endothelial function link remains strong also in a statistical model that included CRP suggests that inflammation-independent pathways play a significant role in the putative effect of UA on endothelial function. Serum uric acid showed an

association with subsequent cardiovascular events and death from all causes. such association was clinically consistent and independent of many potential confounders including age, gender, body mass index, diabetes, TC/HDL-C [20]. At entry into the study, when serum uric acid was determined, all subjects were untreated, important concomitant disease were excluded.

This study has several limitations. The cross-sectional design does not allow establishment of the direction of causality; therefore, our observations remain to be confirmed in prospective observational and interventional studies. Second, ours is a tertiary referral center; therefore, patients who enrolled in this survey represent a selected population that is not representative of primary care. Third, we cannot exclude that UA constitutes a measure of residual confounding from Framingham risk factors, e.g. That relatively higher UA concentration may be the expression of a longer exposure to hypertension and/or to dyslipidemia.

From this study we conclude that hyperuricemia in individuals with essential hypertension is associated with endothelial dysfunction. This association, which is independent of classical risk factors, CRP, supports the hypothesis that UA plays a significant role in this alteration in humans. Interventional studies are needed to clarify the nature of this association.

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