Association of Hyperuricemia With Carotid Intima-Media Thickness, Albuminuria, Diabetes, Hypertension in Chronic Renal Failure

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Abstract

Background: Carotid artery intima-media thickness (CAIMT) measured by B-mode ultrasonography is widely used as a surrogate marker atherosclerosis. Hyperuricemia is also a well recognized risk factor for cardiovascular diseases. This study was done to find out the role of hyperuricemia on CAIMT and albuminuria, diabetes and hypertension in chronic renal failure (CRF) patients.

Methods: 132 CRF patients and 66 age and sex matched healthy controls were included in this study. Out of 132 CRF patients, 35 were hyperuricemic. CAIMT were measured by B-mode ultrasonography. Statistical analyses were done by SPSS (Statistical package for the social Sciences) soft ware (window version 17.0).

Results: Hyperuricemia was independently correlated with CAIMT in CRF patients (P = 0.018). CRF patients with hyperuricemia had significantly higher CAIMT compared to CAIMT of CRF patients without hyperuricemia (P value < 0.001) and healthy controls (P < 0.001). In hyperuricemic CRF patients, prevalence of hypertension (P < 0.001) and diabetes (P = 0.007) was significantly higher than non-hyperuricemic CRF patients.

Conclusions: Hyperuricemia is independently responsible for increased thickening of Carotid artery intima media thickness and also associated with higher level of albuminuria, and higher prevalence of hypertension and diabetes in CRF patients.

Keywords: Carotid artery intima media thickness; Chronic renal failure; Hyperuricemia; Diabetes; Hypertension; Albuminuria

Introduction

Increased thickening of carotid artery intima media thickness (CAIMT) is a mirror of generalized atherosclerosis [1]. CAIMT measured noninvasively by ultrasonography is widely used as a surrogate marker of atherosclerosis [2]. Hyperuricemia (HUA) is an independent risk factor for the progression of renal dysfunction [3, 4] and cardiovascular events [3-5], and 18.4% of female and 25.8% of male patients with hyperuricemia is suffering from chronic renal failure (CRF) [6]. The National Health Examination Survey III-USA demonstrated that serum uric acid (SUA) level > 5.7 mg/dL is an independent risk factor for Coronary artery disease (CAD) and > 7 mg/dL is an independent risk factor for stroke [7]. A higher SUA level is an atherogenic factor [2] but some study did not include the effect of hyperuricemia on CAIMT [8]. Several studies have shown the association between hyperuricemia and microalbuminuria [9] but some study showed there was lack of relationship between SUA and proteinuria [10].

This study was done to find out the role of hyperuricemia on CAIMT and albuminuria in CRF patients.

Materials and Methods

Study subjects

The study subjects included 132 CRF patients, and 62 age and sex matched healthy controls.

CRF patients

Out of 132 CRF patients, 35 were suffering from hyperuricemia, 47 (35.6%) of CRF patients were female and 85 (64.4%) were male. Mean age of CRF patients was 45.96 ± 0.92 years, 59 (44.7%) were smokers and 73 (55.3%) were non-smokers, 36 (27.3%) and 35 (26.5%) were suffering from dyslipidemia and hyperuricemia respectively, 37 (28%) CRF patients had Diabetes. Mean 24 hours total urine albumin excretion and glomerular filtration rate (GFR) were 784.43

Table 1. Demographic Characters and Clinical Data of CRF Patients and Healthy Controls

	CRF Patients	Healthy controls
Number	132	66
Male: Female	85 (64.4%):47 (35.6%)	39 (59.1%):27(40.9%)
Age (years)	45.96 ± 0.92	46.74 ± 1.19
Fasting blood sugar (mg %)	111.01 ± 3.14	85.87 ± 1.25
GFR (mL/min/1.73 m^2)	17.47 ± 0.52	116.74 ± 3.51
24 hours total urine albumin excretion (mg)	784.43 ± 45.23	Not measurable
Smoker: Non-smoker	59 (44.7%):73 (55.3%)	00:66
Dyslipidemic: Non-Dyslipidemic	36 (27.3%):96(72.7)	00:66
Hypertensive: Non-hypertensive	80 (60.6%):53(39.4%)	00:66
Diabetic: Non-diabetic	37 (28%):95(72%)	00:66
Hyperuricemia	35 (26.5%)	00
CAIMT (Micron)	908.91 ± 14.47	707.16 ± 6.79 micron

Abbreviations: GFR, Glomerular filtration rate; CAIMT, Carotid artery intima medial thickness; CRF, Chronic renal failure.

± 45.23 mg and 17.47 ± 0.52 mL/min/1.73 m^2 respectively, 80 (60.6%) were suffering from hypertension (Table 1, 2).

Healthy controls

Out of 62 healthy controls, 39 (59.1%) male and remaining were female. Mean age of the healthy controls was 46.74 ± 1.19 years. All healthy controls were non smokers, non-dyslipidemic, non-hyperuricemic and non-diabetic non-hypertensive, 24 hours total urine albumin excretion was not measurable (Table 1).

After taking consent, all subjects underwent a careful interview, a clinical examination with an evaluation of patient history based on hospital and outpatients records and laboratory investigations.

Both CRF patients and healthy controls had normal body mass index, body weight and waist circumference.

Biochemical measurements

Venous blood was taken in the morning after an overnight fast for at least 12 hours for biochemical analysis. All biochemical tests were performed at department of biochemistry, Burdwan Medical College.

Uric acid measurement

Hyperuricemia was diagnosed when serum uric acid level was > 7 mg/dL in men and > 6.5 mg/dL in women [11]. Uric acid was measured on a standard auto analyzer.

GFR measurement

CRF was identified when glomerular filtration rate (GFR) was < 60 mL/min/1.73 m^2 for consecutive 3 months or more [10]. Glomerular filtration rate (GFR) was estimated with The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula which includes serum creatinine, age, gender and race as variables, with different versions depending on ethnicity, gender and creatinine value [12].

Twenty four (24) hours urine total albumin excretion measurement

Twenty four (24) hours urine total albumin excretion is the "gold stander "for measurement of albuminuria [13] and was measured by Esbach's albuninometer. Microalbuminuria is defined when 24 hours total urine albumin excretion is 30 - 300 mg and when it is > 300 mg, it is called proteinuria or

Table 2. Demographic Characters and Clinical Data of Hyperuricemic and Non-Hyperuricemic CRF Patients

	Hyperuricemic CRF Patients	Non-hyperuricemic CRF Patients
Number	35	97
Male: Female	80%:20%	58.76%:41.23%
Age (years)	45.46 ± 1.06	47.34 ± 1.84
Fasting blood sugar (mg %)	134.88 ± 7.42	102.40 ± 2.89
GFR (mL/min/1.73 m^2)	17.02 ± 1.00	17.64 ± 0.60
24 hours total urine albumin excretion (mg)	1148.71 ± 81.19	652.99 ± 47.73
Smoker: Non-smoker	24 (68.6%):11 (31.4%)	16 (16.5%):81 (83.5%)
Dyslipidemic: Non-Dyslipidemic	20 (57.1%):15 (42.9%)	16 (16.5%):81 (83.5%)
Hypertensive: Non-hypertensive	30 (86.5%):5 (14.3%)	50 (51.5%):47 (48.5%)
Diabetic: Non-diabetic	16 (45.7%):19 (44.3%)	23 (23.7%):74 (76.3%)
CAIMT (Micron)	1051.22 ± 15.60	857.56 ± 15.95

Abbreviations: GFR, Glomerular filtration rate; CAIMT, Carotid artery intima medial thickness; CRF, Chronic renal failure.
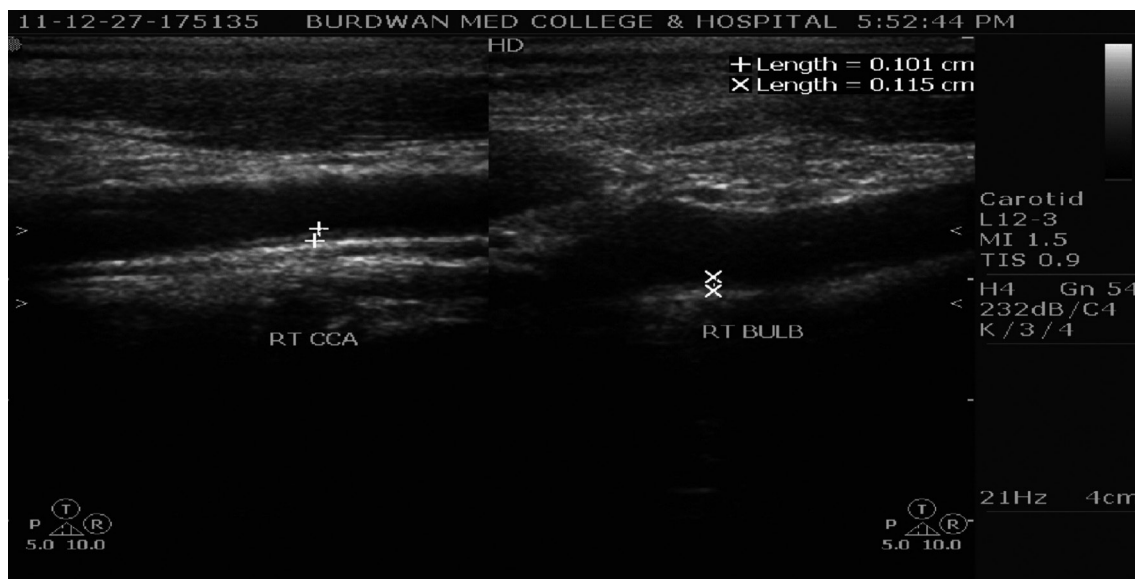
Figure 1. Carotid artery intima media thickness at right common carotid artery (RT CCA) and right carotid bifurcation (RT BULB) in a hyperuricemic CRF patient.

macroalbuminuria [14].

Plasma glucose measurement

Plasma glucose was estimated by a "glucose oxidase-peroxidase" method. Diabetes was diagnosed according to "American Diabetes Association" when a previous or current 12 h fasting glucose level is 7 mmol/L or greater (≥ 126 mg %).

Lipid profile

Serum total cholesterol was measured by "cholesterol oxidase-peroxidase" method. Patients who used cholesterol lowering medication or had a total serum cholesterol level ≥ 200 mg/dL [15] or triglycerides > 200 mg/dL [16] or HDL-C < 40 [17] were classified as having Dyslipidemia.

Anthropometric measurements

Body mass index measurement

Body mass index (BMI) was calculated by using the formula: BMI = weight (in kilograms)/height (in meters)^2. All CRF patients and healthy controls were non-obese (Obesity was defined as a body mass index (BMI) of ≥ 25 kg/m^2) [17].

Blood pressure estimation

Hypertension was diagnosed when a patient had systolic blood pressure (BP) ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg after taking 5 minutes rest or had received medicine for hypertension [18]. The average of three BP measurements was used for final estimation of BP.

CAIMT measurement

CAIMT was performed with a 7 MHz B-mode ultrasound system (Philips-HD7 Diagnostic Ultrasound System, made in China). The IMT was defined as the distance between the leading edge of the luminal echo to the leading edge of the adventitia of the media, was measured at the diastolic phase (Fig. 1). The B-mode scanning protocol included the scanning of the right and left common carotid arteries (3 cm before the carotid bifurcation), carotid bifurcation, as well as of the internal carotid artery 2 cm distally from the carotid bifurcation [19]. Measurements were always performed in plaque-free arterial segments [20].

Others

Hemodialysis

Hemodialyzed patients were identified as who had been on regular hemodialysis treatment (treated thrice weekly) for at least 6 months [21].

Smoking

Participants were classified as non-smokers if they responded that they had smoked fewer than 100 cigarettes or 5 packs of cigarettes during their lifetime [22].

All examinations and measurements were performed by same examiner to exclude examiner bias.

Statistical methods

Chi-square test, Paired t test, independent samples t test, lin-

Table 3. Comparison of CAIMT of Different Groups by Independent Samples t Test

Different groups of CRF patients	CAIMT value (Micron)	P value
Hyperuricemic CRF pt: Non-hyperuricemic pt	1051.22 ± 15.60:857.56 ± 15.95	0.000
Hyperuricemic CRF pt: Healthy Controls	1051.22 ± 15.60:707.16 ± 6.79	0.000

Abbreviations: CRF, Chronic renal failure; CAIMT; Carotid artery intima media thickness. P value < 0.05, statistically significant. P value ≥ 0.05, statistically not significant.

ear multivariate regression analysis with 95 percent confidence interval were performed for data analysis. P value less than 0.05 was taken as statistically significant. Data were expressed as means ± SE (standard Error). All these analysis were performed using a commercially available software SPSS (17th version for window) on personal computer.

Results

Here CRF patients and healthy controls were age (P value = 0.605) and sex (P value = 0.467) matched. CRF patients with hyperuricemia and without hyperuricemia were also age (P value = 0.380) and sex (P value = 0.074) matched.

There was no difference of GFR between CRF patients with hyperuricemia and without hyperuricemia (P value = 0.603).

In this study, 45.71% hyperuricemic CRF patients had diabetes and mean fasting blood sugar in this group 134.88 ± 7.42 mg/dl. 85.71% and 57.14 % CRF patients with hyperuricemia were associated with hypertension and dyslipidemia respectively.

In our study, CRF patients with hyperuricemia had significantly higher CAIMT (1051.22 ± 15.60 micron, P value = 0.000) compared to CAIMT of CRF patients without hyperuricemia (857.56 ± 15.95 micron) (Table 3).

It was also shown that hyperuricemic CRF patients had higher CAIMT (1051.22 ± 15.60 micron, P value = 0.000) than age (P value = 0.786) and sex (P value = 0.058) matched healthy controls (707.16 ± 6.79 micron) (Table 3).

In CRF patients, multivariate regression analysis showed CAIMT was positively correlated with age (P = 0.044), sex (P = 0.07), smoking (P = 0.004), dyslipidemia (P = 0.001), hypertension (P = 0.002), dialysis (P = 0.004), 24 hours total urine albumin excretion (P = 0.002), fasting blood sugar (P = 0.000) and hyperuricemia (P = 0.018), and negatively correlated with GRF (P = 0.000). So, hyperuricemia was independently correlated with CAIMT in CRF patients (Table 4).

Our study documented that hyperuricemic CRF patients had higher albuminuria (1148.71 ± 81.19 g/24 hours, P value

= 0.000) compared to CRF patients without hyperuricemia (652.99 ± 47.73 mg/24 hours).

In hyperuricemic CRF patients, prevalence of hypertension was significantly higher (85.71% P value = 0.000) than non-hyperuricemic CRF patients (51.54%).

Hyperuricemic CRF patients had significantly higher fasting blood sugar (134.88 ± 7.42 mg/dL, P value = 0.000) than CRF patients without hyperuricemia (102.40 ± 2.89 mg/dL). There were also higher prevalence of fasting blood sugar in CRF patients with hyperuricemia than CRF patients without hyperuricemia (P value = 0.007).

Discussion

Kawamato et al [23] and Neogi T et al [24] found that SUA is an independent risk factor of atherosclerosis along with known risk factors such as age, sex, smoking, hypertension, dyslipidemia, etc. Our study also showed same finding. In our study, there was also significantly higher CAIMT in hyperuricemic CRF patients than non-hyperuricemic CRF patients and healthy controls. So, aggressive treatment of hyperuricemia may halt or slow the progression of atherosclerosis in CRF patients.

In concordance with "Normative aging study" [25], El-sayed et al [26], Tavil Y et al [2] our study also demonstrated that the hyperuricemia predicts the development of hypertension. So, controls of hyperuricemia can control hypertension in CRF patients and halt or slow the further progression of atherosclerosis.

Tseng et al [27] and Fukui et al [28] documented that hyperuricemia was associated with increased urinary albumin excretion. But Obermayr RP et al [10] reported that there was lack of relationship between SUA and proteinuria. Our study showed that albuminuria was significantly higher in hyperuricemic CRF patients than non-hyperuricemic CRF patients. So, controls of hyperuricemia can halt or slow the further progression of atherosclerosis by reducing albuminuria in CRF patients.

Viazzi F et al [29], Dehghan A et al [30] and Wiik BP et

Table 4. Linear Multivariate Regression Analysis of Traditional Risk Factors Correlating With CAIMT in CRF Patients.

Independent Variables	t	P value	95.0% Confidence Interval for B	
			Lower Bound	Upper Bound
Age	2.032	0.044	0.035	2.690
Sex	2.769	0.007	12.160	73.148
Smoking	2.948	0.004	16.455	83.721
Dyslipidemia	3.367	0.001	25.957	100.021
Hypertension	3.207	0.002	20.080	84.890
Dialysis	2.957	0.004	18.126	91.566
Glomerular Filtration Rate	-5.699	0.000	-9.769	-4.732
Protein	3.243	0.002	0.021	0.086
Fasting Blood Sugar	3.642	0.000	0.405	1.369
Hyperuricemia	2.401	0.018	7.808	81.195

a. Dependent Variable: CAIMT

al [31] reported that hyperuricemia predict development of new onset diabetes. Our study also showed that Hyperuricemic CRF patients had significantly higher incidence of diabetes than CRF patients without hyperuricemia. So, controls of hyperuricemia can halt or slow the further progression of atherosclerosis by reducing development of new onset diabetes in CRF patients.

There were some limitations in this study because [1] premature atherosclerosis, serum homocysteine, lipoprotein (a), physical activity, atherogenic diet, pro-inflammatory factors and pro-thrombotic factors could not be examined due to the limitations of budget and study design, [2] small numbers of participants were included.

Conclusions

Hyperuricemia is independently responsible for increased thickening of carotid artery intima media thickness and also associated with higher level of albuminuria, and higher prevalence of hypertension and diabetes in CRF patients. So, aggressive control of hyperuricemia may halt or slow the progression of carotid artery intima media thickening in

CRF patients. There is no difference of GFR between CRF patients with hyperuricemia and without hyperuricemia.

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