Original Article

A study on the relationship between serum uric acid and the thickness of intima-mediated carotid

Ahmad Enhesari[1], Manouchehr Khatami[2], Mohammad Hossein Gozashti[3]*, Zohreh Safi[3], Mehrdad Khatami[4, 5]

[1]Physiology Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran. [2]Cardiovascular Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran. [3]Endocrinology and Metabolism Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran. [4]Noncommunicable Research Center, Bam University of Medical Sciences, Bam, Iran. [5]Cell Therapy and Regenerative Medicine Comprehensive Center, Kerman University of Medical Sciences, Kerman, Iran.

Correspondence: Mohammad Hosseini Gozashti, Endocrinology and Metabolism Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran. drgozashti@yahoo.com; m.khatami@mubam.ac.ir

ABSTRACT

Levels of serum uric acid are associated with cardiovascular attacks and high blood pressure. Some researchers have suggested that the serum levels of uric acid may also be related to the thickness of the Intima-mediated carotid. The aim of this study was to evaluate the serum level of uric acid and its relationship with the thickness of Intima-mediated carotid in patients referred to Be'sat Clinic of Kerman. 180 patients, including 86 males and 94 females with an average age of 41.1 ± 3, were studied. In all patients, blood pressure and BMI were measured. Serum levels of uric acid, TG, cholesterol, HDL, LDL, and also the thickness of Intima-mediated carotid was measured and statistically analyzed.

The results of this study showed that the thickness of Intima-mediated carotid significantly correlated with serum uric acid ($p = 0.02$, $r = 0.71$). The results also showed that uric acid levels were related with higher BMI and higher levels of metabolic factors. The results of our study generally show that people with higher serum uric acid have a significantly higher thickness of the Intima-mediated carotid. People with high blood pressure also had higher carotid thickness compared to those with normal blood pressure. Other metabolic factors were higher in people with high serum uric acid than those that have levels of normal uric acid.

Keywords: High blood pressure, Intima-mediated thickness of carotid artery, Serum uric acid, Cardiovascular, Metabolic factors

Introduction

Stroke is one of the reasons for death and long-term disability around the world so that one person suffering from a stroke per second in the United States and every 1/3 minutes someone dies because of it [1, 2]. Every year, hundreds of people die due to brain stroke in Iran. The point is that the disease does not happen suddenly and doctors can identify those who are at risk of it.

Several factors contributing to stroke, such as blood pressure, etc., due to changes in lifestyles and poor eating habits, and the outcomes of all these changes will increase the stroke in the community. About 80% of ischemic stroke cases are due to ambulatory events or stenosis of the cerebellar arteries. In particular, atherosclerotic plaques and arterial stenosis are associated with about 20% to 30% of brain infarction [3, 4].

Atherosclerosis is characterized by an increase in the progressive thickness of the arteries wall. The risk factors for atherosclerosis are divided into two modifiable groups including hyperlipidemia, hyperuricemia, diabetes, smoking, hypertension, and non-modifiable groups including aging, male sex, family background, and genetic abnormalities [5, 6]. In humans, the final oxidative product of purine catabolism is known as Serum uric acid. Various studies indicate a strong association between atherosclerotic disease and serum uric acid [7-12]. Feng *et al.* (2018) [13] studied 564 people in China and

Access this article online	
Website: www.japer.in	**E-ISSN:** 2249-3379

How to cite this article: Enhesari A, Khatami M, Gozashti MH, Safi Z, Khatami M. A study on the relationship between serum uric acid and the thickness of intima-mediated carotid. J Adv Pharm Educ Res. 2021;11(3):83-7. https://doi.org/10.51847/TfjLbFn5kr

suggested that serum uric acid levels are associated with the development and progression of atherosclerotic vascular changes. Serum uric acid contributes to the development of ATs, including endothelial damage, oxidative metabolism, and increased platelet aggregation and adhesion [14, 15]. In another study by Choi *et al.* (2018), the thickness of Intima-Media in patients with high uric acid levels was higher than those with normal uric acid levels. The study also suggested that renal dysfunction in patients with hyperuricemia is associated with an increase in CIMT [16].

Carotid ultrasonography is used as a non-invasive and effective diagnostic method for determining the early stages of atherosclerotic changes in the arterial wall. Intima-media thickness (IMT) measurements and plaque formation are used as early warning and early indicators for early diagnosis of atherosclerosis. For measuring IMT, a high-resolution B-mode ultrasound scanner is used [17, 18].

Since serum uric acid can be effective in developing atherosclerosis, calculating CIMT is an easy method for detecting the presence of atherosclerosis, so the purpose of this study was to determine the relationship between serum uric acid and CIMT.

Materials and Methods

This is a cross-sectional study in which 180 people who participated in Kerman's Coronary Artery disease study II (KERC AD SII) were randomly selected. After obtaining the informed consent of the people, demographic data including age, sex, weight, and blood samples were taken after 14-12 hours of fasting and were kept at room temperature. Then, the blood glucose tests, serum lipids (including HDL triglycerides and cholesterol) were measured by the enzymatic method. Patients with intracranial hemorrhage, subarachnoid hemorrhage, and those with a background of cerebrovascular accident and cardiovascular disease, and uncontrolled blood pressure were excluded. Before completing the questionnaire and sonography, the purpose of the study was completely explained to all participants accurately.

Carotid sonography

Individuals were studied by carotid Doppler sonography at referring time and the thickness of the Intima-Media layer (IMT) was measured using the Philips IU22 ultrasound scanner. During the sonography, a high-resolution B-mode ultrasound scanner was used to measure IMT. In this method, a common carotid artery, carbohydrate Biloba, and internal carotid artery on both sides of the neck were examined for determining the thickest part of the Intima-Media carotid. The sonography scan was done accurately and IMT is defined based on the distance between the edge of the intima lumens from the edge of the advantis media (The distance between the two ecognic lines observed in the B-mode ultrasound) and the mean of the CIMT was calculated through the total thickness of both sides divided by two, and were used in the study, which is briefly described here as CIMT. It should be noted that hyperuricemia is defined by the levels of serum uric acid above 7 mg/dl in men and above 5.7-6 mg/dl in women.

Data analysis

After collecting data, it was analyzed by SPSS version 20 and then statistically analyzed. Descriptive tests were used to analyze the descriptive data and Pearson correlation coefficient analysis was used to analyze the variables related to IMT.

Results and Discussion

180 patients were evaluated totally. Based on the cut-off point, uric acid was considered to be 5.7 for men and 7.7 for men. 22 people had high uric acid and 158 normal serum uric acid. The mean uric acid in the studied patients was 6.0 ± 0.9 **(Table 1)**.

Table 1. Demographic and clinical characteristics of persons in the study

Characteristics	Mean
c-IMT mm, mean (range)	0.53 ± 0.12
Age, years (mean)	41.1 ± 3.1
Body mass index (kg/m2)	28.7 ± 2.1
Fasting plasma glucose (mg/dL)	85.6 ± 11.9
Cholesterol (mg/dL)	186.9 ± 28.8
HDL (mg/dL)	41.9 ± 8.7
LDL (mg/dL)	118.0 ± 25.4
TG (mg/dL)	154.9 ± 89.4
Systolic blood pressure	160.1 ± 3.1
Diastolic blood pressure	87.1 ± 3.1
Uric acid (m mol/L)	6.02 ± 0.9

Plasma measurements are reported as means ± SD. *P o 0.05 by unpaired t-test. HDL: high-density lipoprotein; c-IMT: carotid intima-media thickness; LDL: low-density lipoprotein.

The gender abundance of the persons is described by 86 men (47.7%) and 94 women (52.3%). The mean of intima-media thickness of the carotid artery in studied persons was 0.12 ± 0.53.

The results of the statistical analysis showed a positive linear relationship between serum uric acid and carotid artery thickness (p = 0.02, r = 0.71) **(Figure 1)**.

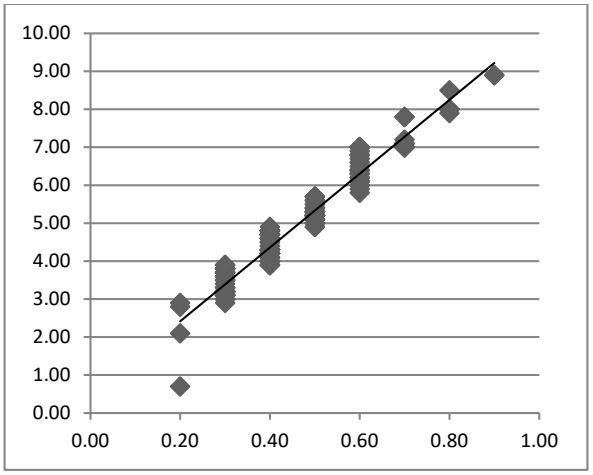

Figure 1. Relationship between Intima Thickness - Carotid Artery media with Serum Uric Acid

The results of the study also suggest that the intima-media thickness of the carotid artery separately and independently has a meaningful linear relationship with BMI, TG, HDL, cholesterol, diastolic blood pressure, Systolic blood pressure, and fasting plasma glucose **(Tables 1 and 2, Figures 2-4)**.

Table 2. Multiple linear regression between various parameters and c-IMT

Characteristics	B	P
Body mass index	0.56	0.03
Fasting plasma glucose	0.83	0.00
Cholesterol	0.78	0.00
HDL	-0.43	0.00
LDL	0.65	0.00
TG	0.70	0.00
Blood pressure	0.83	0.00
Uric acid	0.71	0.02

The regression coefficient (B) represent data and. *P < 0.05. Each parameter was adjusted against all the other parameters presented in this table. LDL: low-density lipoprotein; c-IMT: carotid intima-media- thickness; HDL: high-density lipoprotein.

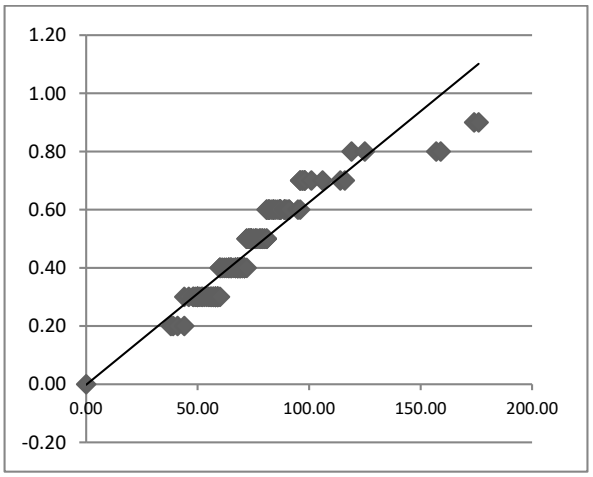

Figure 2. Investigating the relationship between BMI and intima-media thickness

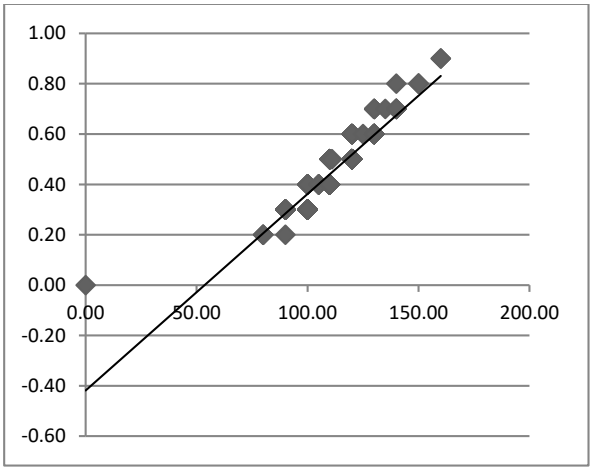

Figure 3. Relationship of Medium Blood Pressure with Intima Thickness and Carotid Artery

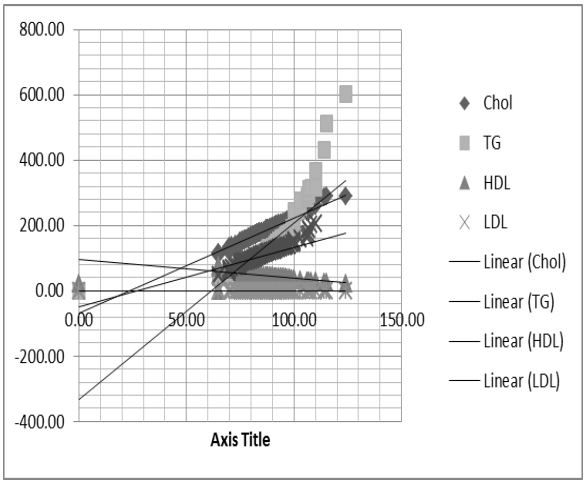

Figure 4. Investigating the relationship between metabolic factors and intima-media thickness of the carotid artery

The results of the study generally indicate that there is a significant relationship between serum uric acid and carotid thickness. According to Santa *et al*. (2018), there is a significant relationship between serum uric acid level and CIMT, which is not dependent on age, the traditional risk (LDL/HDL ratio), and nontraditional risk (inflammation, circumference, and inflammatory factors).

Other studies examine the relationship between the thickness of the intima-media of the carotid artery and the serum uric acid levels. A study by Choi *et al.* (2018), suggested that the thickness of the intima-media in patients with high uric acid is significantly higher than those with normal levels of uric acid. This study also suggested that hyperuricemia is associated with impaired renal function and causes a further increase in CIMT [19]. Nguyen TBT *et al.* (2009) investigated the association between carotid hyperuricemia and cartilage IMT in patients with and without hypertension; cartilage IMT in hypertensive and high uric acid serum had an increased intima-mediated thickness [20]. In another study by Caliskan M *et al.*, the level of uric acid and cartilage IMT hyperuricemia in patients with Masked Hypertension was evaluated and it was found that uric acid levels and carotenoid IMT in these patients were higher than the control group and the higher level of uric acid increases

with the increase of carotid IMT [21]. In another study by Li Q *et al.* (2010), the relationship between the prevalence of atherosclerotic plaques and serum uric acid was investigated and it was found that independent higher levels of uric acid with other risk factors of atherosclerotic are inconsistency with an increase in the prevalence of atherosclerotic plaque [22]. The results of all these studies were consistent with this study.

Blood pressure testing revealed that Intima-Media Carotid thickness was significantly higher in people with high blood pressure than in people with normal blood pressure. Also, there was a significant relationship between the thickness of the intima-media of the carotid artery and BMI, FBS, TG, CHOLESTEROL, HDL, and LDL.

However, studies have shown that high levels of uric acid can contradict the role of neuroprotective role in brain damage. Logaloo *et al.* found that serum concentration at the time of admission had a positive correlation with the clinical improvement of patients with stroke [23]. Seet *et al.* showed that serum urate concentrations had a U-shaped relationship with a poor prognostic factor in acute stroke, whereas no significant correlation was found with the vascular outcome. They stated that uric acid, depending on its serum level, could play both useful and harmful roles in the prognosis of stroke [24]. In a study by Chamaru, it was also investigated that there is an inverse association between neurological deficits in stroke patients with serum uric acid serum levels [23]. Studies reject the association between the levels of serum uric acid and CIMT, including a study by Delhin *et al.* (2018), who suggested that high levels of serum uric acid are associated with calcification in coronary arteries and there is no significant relationship with CIMT [19].

The present study generally indicates more metabolic factors in people with higher concentrations of serum uric acid. In epidemiological studies, the importance of LDL-C as a marker of CHD (cardiovascular disease) has been proven. Although half of the patients with normal CHD have LDLC, and the Tanaka study showed that the LDLC / HDLC ratio was able to predict myocardial infarction and sudden death when LDL is less than 120 mg/dl [25], and there is a significant relationship between CMIT and LDL in many studies [26], but in some studies, this relationship has not been seen [27] and it has more relationship with The lower HDL [27]. Lopes *et al.* (2018) studied 55 patients with an average age of 11.9 years, suggesting a significant correlation with CIMT increase in chronic kidney disease and blood pressure as an independent factor [28].

However, the present study and most of the studies that have been done so far have been confronted with limitations, including the effects of genetic and nutritional differences between individuals, coincident diseases, methodological considerations, outcome measures, time of interventions, etc.

Conclusion

This study generally indicates that people with higher serum uric acid have significantly higher carotid artery intimal-mediated thickness. People with high blood pressure also had higher carotid thickness compared to those with normal blood pressure. Other metabolic factors were higher in patients with high serum uric acid than those with normal uric acid levels.

Acknowledgments: Appreciate all individuals, institutions, and organizations that have helped either in the project process or financially.

Conflict of interest: None

Financial support: Kerman University of Medical Sciences with number: IR.KMU.AH.REC.1397.2607.

Ethics statement: Taken from Ethic committee of Kerman University of Medical Sciences with number: IR.KMU.AH.REC.1397.2607

References

1. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart disease and stroke statistics—2021 update: a report from the American Heart Association. Circulation. 2021;143(8):254-743.
2. Cortesi P, Carla F, Fabiana M, Conti S, Naghavi M, Bikbov B, et al. Trends in cardiovascular diseases burden and vascular risk factors in Italy: The Global Burden of Disease study 1990–2017. Eur J Prev Cardiol. 2021;28(4):385-96.
3. Ramanathan RS, Wisco D, Vela-Duarte D, Zafar A, Taqui A, Winners S, et al. Pre-Hospital Diagnosis in Mobile Stroke Unit. J Stroke Cerebrovasc Dis. 2021;30(7):105801.
4. Phipps MS, Cronin CA. Management of acute ischemic stroke. BMJ. 2020;368:l6983
5. Kumar V, Abbas AK, Aster JC. Robbins and Cotran Pathologic Basis of Disease. 10th ed. Philadelphia, PA: Elsevier, 2021:1-392.
6. Von RK, Hamer M, Wentzel A, Malan L. Circulating neurotrophins and hemostatic risk factors of atherothrombotic cardiovascular disease at baseline and during sympathetic challenge: the SABPA study. Sci Rep. 2021;11:2297.
7. Saito Y, Tanaka A, Node K, Kobayashi Y. Uric acid and cardiovascular disease: A clinical review. J Cardiol. 2021;78(1):51-7.
8. Yu W, Cheng JD. Uric acid and cardiovascular disease: an update from molecular mechanism to clinical perspective. Front Pharmacol. 2020;11:582680.
9. Tai S, Li X, Zhu Z, Tang L, Yang H, Fu L, et al. Hyperuricemia is a risk factor for one-year overall survival in elderly female patients with acute coronary syndrome. Cardiovascular. 2020.2615147.
10. Liu F, Hui S, Hidru TH, Jiang Y, Zhang Y, Lu Y, et al. The prevalence, distribution, and extent of subclinical atherosclerosis and its relation with serum uric acid in

hypertension population. Front Cardiovasc Med. 2021;8:638992.

11. Liu F, Hui S, Hidru TH, Jiang Y, Zhang Y, Katsiki N, et al. Serum Uric Acid and Diabetes: From Pathophysiology to Cardiovascular Disease. Curr Pharm Des. 2021;27(16):1941-51.
12. Butler R, Morris AD, Belch JJ, Hill A, Struthers AD. Allopurinol normalizes endothelial dysfunction in type 2 diabetics with mild hypertension. Hypertension. 2000;35(3):746-51.
13. Nie Q, Zhang X, Hao Z, Wang L, Liu H, Liu C, et al. Impact of Serum Uric Acid Concentration on the Risk of Cardiovascular Disease: A Cohort Study Conducted in Northern China. Arq Bras. 2021. doi:10.36660/abc.20200378
14. Arévalo JC, Gómez JC, Robles N. Cardiovascular risk assessment after one-year acute ischemic stroke based on uric acid levels and renal dysfunction. A clinical study. Int J Neurosci. 2021;131(6):609-14.
15. Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension. 2003;41(6):1183-90.
16. Choi S, Park J, Song JS, Kang EJ, Lee KH. SAT0372 Increased carotid intima-media thickness in hyperuricemic individuals may be explained by hyperhomocysteinemia associated with renal dysfunction. BMJ Publishing Group Ltd; 2018.
17. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson Jr SK. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. N Engl J Med. 1999;340(1):14-22.
18. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation. 2007;115(4):459-67.
19. Dehlin M, Drivelegka P, Sigurdardottir V, Angerås O, Jacobsson L, d'Elia HF. FRI0228 Urate correlates to coronary artery calcification but not to intima-media thickness. BMJ Publishing Group Ltd; 2018.
20. Nguyen TBT, Honchar O. The Association between Hyperuricemia and Carotid Intima-Media Thickness in Patients with and without Hypertension. 2015.
21. Ma M, Wang L, Huang W, Zhong X, Li L, Wang H. Meta-analysis of the correlation between serum uric acid level and carotid intima-media thickness. PloS one. 2021;16(2):e0246416.
22. Li Q, Zhou Y, Dong K, Wang A, Yang X, Zhang C, et al. The association between serum uric acid levels and the prevalence of vulnerable atherosclerotic carotid plaque: a cross-sectional study. Sci Rep. 2015;5:10003.
23. Aliena-Valero A, Rius-Pérez S, Baixauli-Martín J. Uric acid neuroprotection associated to IL-6/STAT3 signaling pathway activation in rat ischemic stroke. Mol Neurobiol. 2021;58(1):408-23.
24. Seet RC, Kasiman K, Gruber J, Tang SY, Wong MC, Chang HM, et al. Is uric acid protective or deleterious in acute ischemic stroke? A prospective cohort study. Atherosclerosis. 2010;209(1):215-9.
25. Kobayashi T, Nakamura T, Uematsu M, Horikoshi T, Yoshizaki T, Watanabe Y, et al. Evaluation of renal tubulointerstitial damage as a residual renal risk factor for adverse cardiac events in patients with myocardial infarction. J Cardiol. 2021;78(2):114-9.
26. Yang C, Sun Z, Li Y, Ai J, Sun Q, Tian Y. The correlation between serum lipid profile with carotid intima-media thickness and plaque. BMC Cardiovasc Disord. 2014;14(1):181.
27. Vijayasarathi A, Goldberg SJ. Comparison of carotid intima-media thickness in pediatric patients with metabolic syndrome, heterozygous familial hyperlipidemia, and normals. J Lipids. 2014;2014.
28. Lopes R, Morais MB, Oliveira FL, Brecheret AP, Abreu AL, Andrade MC. Evaluation of carotid intima-media thickness and factors associated with cardiovascular disease in children and adolescents with chronic kidney disease. J Pediatr. 2019;95(6):696-704.