Original Research Article

Serum uric acid, lipid profile and alkaline phosphatase levels in ischemic cerebrovascular accident patients

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Received: 06 June 2021
Accepted: 14 July 2021

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ABSTRACT

Background: Stroke or cerebrovascular accident (CVA) is noted as the second cause of mortality, especially in the elderly population. Recent studies indicated that higher concentrations of uric acid are involved in various vascular diseases. The findings of previous investigations suggest that, elevated serum alkaline phosphatase (ALP) levels may have a pathophysiological character in the occurrence of atherosclerotic vascular disease (AVD) of the heart and brain. This study evaluated the association between serum uric acid (SUA) levels, serum lipid levels, serum alkaline phosphatase (ALP) levels, and changes in ischemic cerebrovascular accident patients.

Methods: All patients with Ischemic cerebrovascular accident age >50 years were included based on their clinical, laboratory, and radiological findings (including computed tomography (CT)/magnetic resonance imaging (MRI)) those admitted in our hospital. As control group 200 healthy individuals matched for sex and age were recruited from the same demographic area.

Result: Multiple logistic regression analysis findings proposed four components as significant predictors in ischemic cerebrovascular accident (serum uric acid, serum ALP, LDL and HDL). In this study, it was found, that patients with ischemic cerebrovascular accident had significant difference (p<0.001) in serum uric acid and serum ALP than normal patients (non-ischemic cerebrovascular accident patients).

Conclusions: Patients with ischemic cerebrovascular accident had significant difference (p<0.001) in SUA and serum ALP than normal patients (non-ischemic cerebrovascular accident patients). High SUA levels were observed to be associated significantly with ischemic stroke. On the basis of our study design, we cannot clarify that the elevated levels are the risk of ischemic stroke and it requires further studies.

Keywords: Serum uric acid, Serum lipid, Serum ALP, Ischemic cerebrovascular accident

INTRODUCTION

Stroke or cerebrovascular accident (CVA) is defined as an abrupt onset of a neurological deficit that is attributable to a focal vascular cause. The definition of stroke is, clinical and laboratory findings including imaging of brain are used to support the diagnosis.1 The clinical appearances of stroke are highly unpredictable because of the dense anatomy of the brain and its vasculature. Cerebral ischemia is originated by decrease in blood flow that last longer than several seconds.1 The stroke or cerebrovascular accident (CVA) is noted as the second cause of mortality, especially in the elderly population.2 Pre-existing heart illnesses such as coronary artery disease (CAD) and atrial fibrillation, smoking, diabetes mellitus, hypertension, dyslipidaemia, and age more than 65 years are the major risk factors of CVA.3 Circulating molecules and some biochemical factors have been introduced as risk factors for vascular diseases.

Recent studies indicated that higher concentrations of uric acid (UA) are involved in various vascular diseases. Hyperuricemia have also been proposed as a factor in the
pathogenesis of an atheroma. The important association was observed between SUA and serum triglycerides, this implicates that a rise in SUA and serum triglyceride may play specific role in the etiology of ischemic cerebrovascular disease.\(^4\) SUA (pKa 5.8) is spread throughout the extra-cellular fluid section as sodium urate and cleared from the plasma by glomerular filtration. The proximal renal tube reabsorbed around 90% of filtered UA, while active secretion into the distal tube by an ATPase-dependent mechanism contributed to overall clearance. Serum UA concentration within the population has a typical reference range (95% CI) of 120–420 μmol/L.\(^6\)\(^7\) Hyperuricemia is an abnormally high level of UA in the blood. In humans, 360 μmol/L (6 mg/dL) and 400 μmol/L (6.8 mg/dL) is the upper end of the normal range of SUA for women and men respectively. Xanthine oxidase activity and UA synthesis are elevated in vivo under ischemic conditions and elevated serum UA may act as a marker of underlying tissue ischemia. UA crosses dysfunctional 2 endothelial cells and accumulates as crystals within atherosclerotic plaques.

Alkaline phosphatase (ALP) is generally considered as a clinical marker of bone or liver disease, such as vitamin D deficiency and cholestasis.\(^3\) However, ALP can catalyse the hydrolysis of organic pyrophosphate and promote vascular calcification.\(^5\) Previous studies have found that higher levels of ALP are associated with poorer functional outcomes and mortality in patients with stroke.\(^9\)\(^,\)\(^10\) Serum is a reliable clinical specimen and its collection is relatively non-invasive. The majority of alkaline phosphatase in serum (more than 80%) is released from liver and bone, and in small amounts from the intestine. Even though ALP is present in many tissues in whole body, their precise physiological function remains largely unknown.\(^11\)\(^,\)\(^12\) On the light of these points this current study was planned to evaluate the association between serum uric acid (SUA) levels, serum lipid levels, serum alkaline phosphatase (ALP) levels, and changes in ischemic cerebrovascular accident patients.

**METHODS**

This case control study was done over a period of January 2019 to October 2020 in the department of medicine, GSVM medical college, L.L.R.H and associated hospitals Kanpur on ischemic cerebrovascular accident patients after clearance from institutional ethical committee. Patients with ischemic cerebrovascular accident with more than 50 years of age were recruited based on their clinical, laboratory, and radiological findings (including CT/MRI). Patients with age less than 50 years, chronic intake of hyper-uricemic drugs, any conditions which alter serum uric acid levels (lymphoproliferative diseases, polycythemia, myeloproliferative disorders, diabetic ketoacidosis, lactic acidosis), and those who did not give consent for study were excluded from the study.

A total 400 patients were examined in this study. 200 patients with ischemic cerebrovascular accident as cases and equal 200 non ischemic cerebrovascular accident people were recruited in the study as controls.

**Methodology**

An informed consent was taken either from the patient or their relatives before interview, examination and investigation. The controls were the blood donors from the study hospital. The controls had no clinical evidence of any cerebrovascular disease. All the required details about cases such as demographic data (age, gender, address, registration number, etc), clinical presentations (signs and symptoms), general 23 examination findings, systemic examination and ischemic cerebrovascular accident, SUA and serum ALP findings were carried out. Blood samples were taken from all patients with acute stroke during 24 hours of admission to check uric acid level, serum ALP, Fasting blood sugar and lipid profile.

All patients (cases) were examined by a qualified neurologist, and ischemic stroke was differentiated by computer tomography (CT) scan and magnetic resonance imaging (MRI). All the patients underwent CT scan as well as MRI.

Diabetes mellitus was defined as HbA1C >6.5 gm% or history of receiving treatment for diabetes mellitus or previously diagnosed diabetes mellitus.

Diabetes was diagnosed if fasting plasma glucose was >110 mg/100 ml or patient was on anti-diabetic medications.

**Biochemical measurements**

The uricase method was used to measure SUA levels, the standard procedures were performed for all other biochemical findings. ALP activity was measured using a Cobas integra 400 Plus automatic bio chemical analyser with matched reagent kits (Roche, Basel, Switzerland). Serum HDL, TG, and LDL, which were estimated calorimetrically using appropriate wave-length filters. The 12 hours to 14 hours fasting samples (approximately 5 ml of whole blood) were taken within 24 hours of admission from the patients, i.e., on the 1st day. For in vitro quantitative determination of activity of lipid fractions in serum following kit methods were performed (Sigma diagnostics (India) Pvt. Ltd., Baroda kit was used).\(^13\)

**Statistical analysis**

Data was analysed using statistical package of social sciences (SPSS, 23.0) software and expressed as mean±standard deviation. Inter group or intra group comparisons were done using independent sample test for comparison of mean values. Mann-Whitney U test (a nonparametric test) was used for comparison of mean values of serum UA in cases and controls. Association between variables was considered statistically significant if p<0.05.
RESULTS

Demographic data of all patients was represented in Figure 1 and 2. The mean age of all patients was 56.56±4.10 years whereas it was 56.46±3.83 years and 56.66±4.36 years for cases and controls respectively (p>0.05). Majority 54.5% of patients were belonging to 51-60 years of age for cases where as for controls it was 42.5% patients with less than 55 years of age (Figure 1).

In cases (out of 200), male and females were 132 (66.0%) and 68 (34.0%) of patients respectively. In controls (out of 200), male and females were 124 (62.0%) and 76 (38.0%) of patients respectively (Figure 2). Mean Hb (%) and HbA1c of all patients was 12.15±1.78 and 5.53±0.97 respectively.

In lipid profile findings, mean serum cholesterol, mean TG and mean LDL was found more in cases than controls. The lipid profile levels were found to be significantly higher in cases than controls except HDL (Table 1). The association of lipid profile parameters among both groups was statistically highly significant (p<0.01) (Figure 3).

Mean SUA and serum ALP levels were more in cases than controls and it was found to be statistically highly significant (p<0.01) (Table 2). SUA and serum ALP was showed non-significant difference among male and females of case group (p>0.05) (Table 3). Multiple logistic regression findings proposed four aspects as significant predictors in ischemic cerebrovascular accident [SUA, serum ALP, LDL and HDL as p<0.001] (Table 4).

The patients with ischemic cerebrovascular accident had significant difference (p<0.001) in SUA and serum ALP than normal patients (non-ischemic cerebrovascular accident patients).

Table 1: Lipid profile levels in cases and controls.

| Lipid profile parameters | Groups | Total | P value |
|--------------------------|--------|-------|---------|
|                          | Cases (n=200) | Controls (n=200) |       |
| Serum cholesterol (mg/dl)| 142.84±25.42 | 124.04±28.61 | 133.44±28.62 | <0.001 |
| TG (mg/dl)               | 132.78±23.51 | 115.06±20.02 | 123.92±23.54 | <0.001 |
| LDL (mg/dl)              | 101.77±27.44 | 85.17±12.38 | 93.47±22.83 | <0.001 |
| HDL (mg/dl)              | 40.08±5.23 | 46.46±6.59 | 43.27±6.75 | <0.001 |
DISCUSSION

Most epidemiological studies have reported a significant association between elevated SUA and increased cerebrovascular disease.14 Although uric (UA) acid is one of the most significant antioxidants in plasma or serum and it appears to be neuro-protective in animal models, the findings from human studies are controversial.15 In acute ischemic stroke serum UA levels would change clearly in association with the level of oxidative stress. A meta-analysis of 16 prospective cohort studies having 230,000 patients reported that the increased serum UA level (in more than 18 years of age patients) is associated ordinary with less than 65 years of age. The mean of all patients was 56 to 60 years of age followed by 154 (38.5%) of patients were in between 51 to 55 years of age. Only 19 (4.8) patients were more than 65 years of age. The mean of all patients was 56.56±4.10 years whereas it was 56.46±3.83 years and 56.66±4.36 years for cases and controls respectively. In our study, most 183 (45.8%) of patients were in between 51 to 60 years of age followed by 154 (38.5%) of patients were in between 51 to 55 years of age. Only 19 (4.8) patients were more than 65 years of age. The mean of all patients was 56.56±4.10 years whereas it was 56.46±3.83 years and 56.66±4.36 years for cases and controls respectively. In controls (out of 200), male and females were 124 (62.0%) and 76 (38.0%) of patients respectively. In cases (out of 200), male and female respectively; in the control group, 60 (68.09%) were male and 174 (31.6%) were female; in stroke patients, 376 (68.4%) were male and 130 (48.8%) were male [in stroke patients, 70 (52.6%) and 63 (47.4%) were male], and 174 (31.6%) were female; in the control group, 373 (67.8%) were male and 171 (31.1%) were female. These differences could be geographical changes of study and inclusion criteria of studies. In our study, mean Hb and HbA1c of all patients was 12.15±1.78 and 5.53±0.97 respectively. The correlation of Hb and

In our study, most 183 (45.8%) of patients were in between 56 to 60 years of age followed by 154 (38.5%) of patients with less than 55 years of age. Only 19 (4.8) patients were more than 65 years of age. The mean of all patients was 56.56±4.10 years whereas it was 56.46±3.83 years and 56.66±4.36 years for cases and controls respectively. The comparison of mean age of both groups was found to be statistically non-significant (p>0.05). Previous study of Talebi et al studied 266 participants, of them, 133 patients had ischemic stroke and 133 were without ischemic stroke.20 The overall mean age of patients was 66.65±9.80 years. The mean age of the participants was found non-significant difference between the two groups as present study finding (67.52±12.21 vs. 65.78±7.40, p=0.08). Talebi et al study showed that patients with a higher serum level of UA are at an increased risk of ischemic stroke with 1.48 odds ratio.20 Another study of Koppula et al the sample size was 1100 participants, of them, 550 (50.0%) patients had ischemic stroke and rest 550 (50.0%) were without ischemic stroke, in this study, mean age of cases controls was 49.3±17.34 years and 47.01±16.78 years respectively (p>0.05).21 In the study of Jia et al a total of 1019 patients were studied, the mean age of 523 cases was 65.6±11.1 years and the mean age of 496 controls was 62.3±10.5 years.22

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Out of total, majority 256 (64.0%) of patients were male and 144 (36.0%) of patients were female. In cases (out of 200), male and females were 132 (66.0%) and 68 (34.0%) of patients respectively. In controls (out of 200), male and females were 124 (62.0%) and 76 (38.0%) of patients respectively. Our results were in accordance with Talebi et al study, 136 (51.2%) were female and 130 (48.8%) were male [in stroke patients, 70 (52.6%) and 63 (47.4%) were male [in stroke patients, 70 (52.6%) and 63 (47.4%) were male], and 174 (31.6%) were female; in the control group, 60 (45.1%) were male and 73 (54.9%) were female, with no statistically significant difference between the groups (p=0.22).20 Another study of Koppula et al reported low rate of female patients as 345 (31.36%) patients and 749 (68.09%) were male.21 In stroke patients, 376 (68.4%) participants were male, and 174 (31.6%) were female; in the control group, 373 (67.8%) were male and 171 (31.1%) were female. These differences could be geographical changes of study and inclusion criteria of studies. In our study, mean Hb and HbA1c of all patients was 12.15±1.78 and 5.53±0.97 respectively. The correlation of Hb and

| Parameters | Groups | P value |
|------------|--------|---------|
| Serum uric acid (mg/dl) | Cases (n=200) | Controls (n=200) | Total | <0.001 |
| 6.83±1.07 | 5.21±0.76 | 6.02±1.23 |
| Serum ALP | 294.6±71.69 | 225.0±44.78 | 259.8±69.12 | <0.001 |

| Parameters | Groups | P value |
|------------|--------|---------|
| Serum uric acid (mg/dl) | Male (n=132) | Female (n=68) | 0.656 |
| 6.85±1.06 | 6.78±1.09 |
| Serum ALP | 296.18±74.12 | 291.54±67.14 | 0.666 |

| Variables | B | S.E. | OR (95% C.I.) | P value |
|-----------|---|-----|--------------|---------|
| Serum uric acid | -1.470 | 0.194 | 0.157 | 0.337 | <0.001 |
| Serum ALP | -0.017 | 0.003 | 0.977 | 0.990 | <0.001 |
| Serum cholesterol | -0.003 | 0.008 | 0.982 | 1.012 | 0.703 |
| TG | -0.011 | 0.010 | 0.971 | 1.008 | 0.252 |
| LDL | -0.042 | 0.012 | 0.937 | 0.980 | <0.001 |
| HDL | 0.160 | 0.031 | 1.105 | 1.246 | <0.001 |
HbA1c among cases and controls was found to be statistically non-significant (p>0.05).

In our study, mean serum cholesterol (mg/dl), mean TG (mg/dl), mean LDL (mg/dl) and mean HDL (mg/dl) of total patients were 133.44±28.62, 123.92±23.54, 93.47±22.83 and 43.27±6.75 respectively of all patients whereas mean serum cholesterol (mg/dl) in cases and control groups was 142.84±25.42 and 124.04±28.61 respectively. Mean TG (mg/dl) in cases and control groups was 132.78±23.51 and 115.06±20.02 respectively. Mean LDL (mg/dl) in cases and control groups was 101.77±27.44 and 85.17±12.38 respectively. Mean HDL (mg/dl) in cases and control groups was 40.08±5.23 and 46.46±6.59 respectively. The lipid profile levels were found to be significantly elevated in cases than controls except HDL and the correlation of lipid profile parameters among cases and controls were found to be statistically highly significant (p<0.01).

Similar pattern of findings was reported by Talebi et al that mean TG (mg/dl), mean LDL (mg/dl) and mean HDL (mg/dl) of total patients were 114.5, 111.0 and 38.0 respectively.20 Mean TG (mg/dl) in cases and control groups was 110.5 and 122.5 respectively. Mean LDL (mg/dl) in cases and control groups was 97.0 and 124.5 respectively. Mean HDL (mg/dl) in cases and control groups was 36.5 and 42.0 respectively. Koppula et al reported mean TG (mg/dl) in cases and control groups was 178.5±40.02 and 138.68±45.3 respectively.21 Mean HDL (mg/dl) in cases and control groups was 53.25±20.23 and 59.56±22.62 respectively. In all the above studies the lipid profile levels were found to be significantly elevated in cases than controls except HDL and the correlation of lipid profile parameters among cases and controls were found to be statistically highly significant (p<0.01).

Comparison of SUA and serum ALP among cases and controls

Uric acid is a weak organic acid, and it is naturally generated in the human body as the end result of purine catabolism from xanthine, and hypoxanthine, and it has long been considered an anti-oxidant reagent.23 Because of its important capacity as an anti-oxidant, it behaves as a free radical scavenger, and therefore, may have a protective role in dysfunction and vascular inflammation.24 The amount of the ischemic infarct and consequently the severity of the stroke event have been reported to be higher in patients with reduced antioxidant activity. Since the level of free radicals is extremely difficult to quantify in the human body, UA can be taken as a major biomarker of the free radical level, which has been determined as a correct measure of the volume of free radicals generated in the body.

Early studies investigating a possible association between SUA and clinical outcome showed mixed results. However, a potential limitation of these studies may be a wider time window for serum UA measurements (e.g., up to 48 and 72 hours). The study carried out by Weir et al showed that serum UA level predicts poor outcome after ischemic stroke.26

In our study, mean SUA and mean serum ALP of total participants was 6.02±1.23 mg/dl and 259.80±69.12 mg/dl respectively. Mean SUA in cases and controls was 6.83±1.07 mg/dl and 5.21±0.76 mg/dl respectively. Mean serum ALP was in cases was 294.61±71.69 mg/dl and in controls was 225.0±44.78 mg/dl. It was observed that SUA and serum ALP level was more in cases than controls. The correlation of SUA and serum ALP levels among the both groups was found to be statistically highly significant (p<0.01). Talebi et al reported mean serum uric acid of total participants was 4.4 and Mean serum uric acid in cases was 4.9 and in controls was 3.9.20 The difference in mean serum uric acid levels between cases and controls was found to be statistically significant (p<0.5). Koppula et al reported mean serum uric acid in cases was 6.14±1.68 and in controls was 4.12±2.20.21 The difference in mean serum uric acid levels between cases and controls was found to be statistically significant (p<0.05), and stated that high serum UA levels were observed to be associated significantly with ischemic stroke, stroke subtypes. Another study by Amin et al reported the mean UA serum level was 7.23.8 mg/dl, which was statistically significantly greater in the control group (p<0.001).

There are limited studies on the connection or association of serum UA levels with stroke risk and stroke sub types. There is rarely any study from India that evaluating the association of serum UA with ischemic stroke. To the best of our knowledge, this is the first study (from Uttar Pradesh), to analyse the association of serum UA and lipid profile parameters with ischemic stroke, and its clinical outcome. A similar prospective study was done by Logallo et al at Haukeland university hospital, Norway which revealed bad outcomes in patients of ischemic stroke with increased serum UA levels.27 Another study carried out by Miedema et al also confirmed these findings.28 However, some studies were reported that decreases in serum UA during the first week after onset of stroke correlates with more severe stroke, unfavourable stroke development, and bad long-term stroke outcome.29,30

Multiple logistic regression analysis to predict ischemic stroke as per the studied variables

Multiple logistic regression analysis model proposed four factors as significant predictors in ischemic cerebrovascular accident [Serum uric acid, serum ALP, LDL and HDL as p<0.001]. In present study, it was found that patients with ischemic cerebrovascular accident had significant difference (p<0.001) in serum uric acid and serum ALP than normal patients (non-ischemic cerebrovascular accident patients). In the study of Talebi et al found two factors as significant predictors in stroke patients including vitamin D in multiple logistic regression analysis model (p=0.007) and UA (p<0.001) after adjusting for hyperlipidemia, diabetes, hypertension,
cigarette smoking, and addiction. The strength of the study was this was a prospective study with blinding of those who assessed the follow-up events.

There are some limitations of this study that are the associations presented in this study might be confounded by unknown factors. The results from this study are restricted by the small sample size and lack of a cohort to control our findings.

**CONCLUSION**

We found that patients with ischemic cerebrovascular accident had significant difference (p<0.001) in SUA and serum ALP than normal patients (non-ischemic cerebrovascular accident patients). Elevated serum UA levels were observed to be associated significantly with ischemic stroke in patients. Based on our study design, we cannot explain absolutely that the elevated levels are the risk of ischemic stroke and it requires further studies.

**ACKNOWLEDGEMENTS**

Author would like to thanks and must express my deepest gratitude to HOD Dr. Richa Giri, department of medicine, GSVM medical college, Kanpur, for allowing me to work in institution and extending valuable help when needed.

**Funding:** No funding sources

**Conflict of interest:** None declared

**Ethical approval:** The study was approved by the Institutional Ethics Committee

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Cite this article as: Gupta G, Kishor S, Kumar A. Serum uric acid, lipid profile and alkaline phosphatase levels in ischemic cerebrovascular accident patients. Int J Adv Med 2021;8:1171-7.