# Elevated Serum uric level is a risk factor for Acute Ischemic Stroke: A case control study from Northern India

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# Abstract

**Background** Elevated Serum uric acid (SUA) is strongly associated with cardiovascular risk factors such as dyslipidemia. It, however, is debated whether it itself is a risk factor of stroke. We therefore investigated the relation between serum UA levels and acute ischemic stroke.

**Material and Methods** A case-control study on patients with acute ischemic stroke presenting at MM Institute of Medical Sciences & Research, Mullana, Haryana, North India was carried out from July, 2019 to September, 2020. The controls consisted of normal individuals attending the OPD similar to the cases in terms of age and gender. Serum levels of uric acid, lipid profile and other biochemical investigations of the cases were carried in the first 24 hours of admission.

**Results** Out of the total 50 cases and 50 controls, 27(54.0%) were males and rest 23(46.0%) were females. Mean ages of the cases and the controls were 60.46 ±12.30 and 60.21±12.12 years respectively. The mean serum uric acid level of the cases was 6.49±2.36 mg/dL whereas mean serum uric acid level of the controls was 5.59±0.98 mg/dL, the difference being statistically significant(p=0.01). Similarly, 22(44.0%) out of the 50 cases were hyperuricemic whereas only 8(16.0%) out of the 50 controls were hyperuricemic, the difference in prevalence being statistically significant too(p=0.002). Dyslipidaemia was found in 40 (80.0%) cases as compared to 10(20.0%) controls(p<0.0001)

**Conclusion** Elevated SUA level is significantly associated with the occurrence of acute ischemic stroke and may be considered a risk factor for acute ischemic stroke.


# Introduction

After coronary heart disease and cancer, stroke is the third leading cause of death globally especially among the elderly. [1, 2] The mortality rate for stroke patients is over 20%, especially in its acute phase and remains higher for several years after the acute event is over compared to general population.[1] Stroke is the second most common cause of morbidity and long-term disability after dementia in adults aged ≥ 65 years worldwide. Around 25% of patients who survives acute stroke develops dementia.[3] Patients who survive acute stroke, around 40% of them are not expected to regain their full independence and self-care, also 25% of them are unable to walk independently.[1]

Hyperuricemia i.e. elevated serum uric acid level has been found to be involved in the pathophysiology of several diseases such as gout, chronic kidney disease and cardiovascular diseases.[4,5] Elevated serum uric acid (EUA) is well known to be associated with several established cardiovascular risk factors such as hypertension, obesity, metabolic syndrome, dyslipidaemia, diabetes mellitus, insulin resistance, chronic kidney disease, etc. [6] On the other hand, uric acid has been known to exert neuroprotective effects by acting as a free radical scavenger. [7, 8]

Since SUA has been found to be frequently elevated in subjects with other established cardiovascular disease risk factors [9,10], it has been widely debated whether UA is an independent cardiovascular disease risk factor through an ability to induce inflammatory and vascular mechanisms, or whether UA may be simply “marking” subjects with other causal risk factors. [9-13]

Prior studies of the relation between UA and stroke incidence have been inconsistent. [14–22] Some studies reported a positive independent relation between UA and stroke [14–18]; others demonstrated that UA did not relate significantly to stroke occurrence. [19-22]

Considering these conflicting data, we undertook this study to evaluate serum uric acid and serum lipid profile levels in patients with ischemic cerebrovascular stroke.

# Material And Methods

*Study design & Settings*

This case-control study was carried out at the Department of Internal Medicine, MM Institute of Medical Sciences & research, Mullana, a tertiary care teaching hospital in district Ambala, Haryana north India between August, 2019 to September, 2020. More than 1000 stroke patients per year are admitted and cared for at this hospital. All the stroke patients admitted in the in-patient department of Internal Medicine/Neurology were regarded as the study population.

*Cases and controls*

Cases were recruited consecutively from patients who were admitted within 24 hours of an acute ischemic stroke in the in-patient department. Ischemic stroke was confirmed by computed tomography scan and/or magnetic resonance imaging of the brain. After confirmation of the ischemic type of stroke, each patient was assessed through both physical examination and clinical investigations before enrolling into the study. Patients were excluded if they had any of the followings- a known or possible cardiac source of emboli or atrial fibrillation; having history of vascular disease, active infections, renal disease (estimated glomerular filtration rate <60 ml/min), liver disease, or thyroid dysfunction; history of Alzheimer’s disease (AD), Huntington’s disease (HD), Parkinson’s disease (PD), or Multiple Sclerosis (MS); or under medications that are known to affect serum uric acid levels such as loop diuretics, salicylates, pyrazinamide, probenecid, ACE inhibitor, or benzbromarone. Same exclusion criteria were applied while selecting controls. For each case, one control was selected from patients attending the out-patient department who had no history of previous stroke and which was confirmed by clinical examinations. Controls were matched with the cases in terms of both age (±5 years) and sex.

*Data collection and variables analyzed*

Data were collected administering a pre-tested questionnaire through face-to-face interviews. For laboratory variables, 5 ml venous blood was drawn from each participant after an overnight fasting of at

least 8 hours to measure fasting blood glucose, serum lipid profile, and SUA. Tourniquet was used but was released just before sampling to avoid artificial increase in the concentration of serum lipids. For oral glucose tolerance test (OGTT), another blood sample was collected after 2 hours of 75 grams oral glucose load. Blood glucose was measured by glucose-oxidase method and rest of the measurements were assessed by standard enzymatic method using automated biochemical analyser (Beckman Coulter AU480, Tokyo, Japan). All the lab tests were done in the mentioned hospital settings within a few hours of sample collection. Care was taken to exclude the haemolysed serum.

A participant was considered having diabetes mellitus (DM) if diagnosed by OGTT (fasting blood glucose value ≥ 7.0 mmol/L and/or 2-h post-load glucose concentration ≥ 11.1 mmol/L) [23] or currently receiving treatment for DM.

SUA level was recorded in mg/dL and can be converted to μmol/L by multiplying with 59.485. Although consensus on the definition of hyperuricemia is scarce [24], serum uric acid levels ≥ 7 mg/dL in men and SUA ≥ 6.5 mg/dl in women were considered as Hyperuricemia.[25]

Dyslipidemia was diagnosed following Japan Atherosclerosis Society guideline [26] where a participant was considered having Dyslipidaemia if any of the following criteria was met :

serum low density lipoprotein (LDL)-cholesterol ≥ 140 mg/dl or high-density lipoprotein (HDL)-cholesterol < 40mg/dl or triglyceride ≥ 200mg/dl.

Participant was considered hypertensive if clinically diagnosed (systolic blood pressure (BP) ≥ 140 mm of Hg and/or diastolic BP ≥ 90 mm of Hg) or currently receiving medication for hypertension (HTN). Participant was considered having coronary heart disease (CHD) if one had the history of angina or infarction (ischemic heart disease) which was later confirmed by chest X-ray, ECG, and echocardiography.

*Ethical consideration*

Ethical approval was obtained from the Ethical Review Board of MM Institute of Medical Sciences & Research, MM Deemed University (MMIMSR/NRCE/2013-2016/637). Informed written consents were obtained from all participants prior to data collection after duly informing about the study and its objectives.

*Statistical analysis*

Qualitative variables were expressed by frequency and percentage, and quantitative variables by mean with standard deviation (SD). Comparison of distribution of categorical data among case and control groups was performed by Chi-square($\chi^2$) test and continuous data by independent t-test. Pearson co-relation coefficient(r) was used to find co-relation between two continuous variables. All the analysis was performed using SPSS version 23.0 and p-value was considered significant at 5% level i.e., <0.05.

# Results

A total of 100 participants, 50 cases and 50 age-and sex-matched controls, were recruited for the study prospectively over the study period.

Background ccharacteristics of the study population are shown in Table 1. mean age of the cases was 60.46 ±12.30 years was the mean of the controls was 60.21±12.12 years. Among the participants, 44 percent of the cases were found to have Hyperuricemia while only 16 percent of controls fell into this category (Fig.1). There was no significant difference in the mean age, age-groups and sex status between the case and control group. Dyslipidemia was observed significantly higher among the cases compared to the controls ($p<0.0001$). There was a significant difference in mean SUA level between cases (6.03 ± 1.84 mg/dl or 358.58 ± 109.31 μmol/L) and controls (4.34 ± 1.60 mg/dl or 258.27 ± 95.36 μmol/L) (Table 2).

**Table 1- Characteristics of the study population (N=100)**

| Variables | Group | | p-value |
|---|---|---|---|
| | Case(n=50) | Control(n=50) | |
| **Mean age (in years)** | 60.46 ±12.30 | 60.21±12.12 | 0.89 |
| **Age-groups (in years)** | | | |
| 25-40 | 04(8.0) | 04(8.0) | 1.0 |
| 41-55 | 18(36.0) | 18(36.0) | |
| 56-70 | 19(38.0) | 19(38.0) | |
| 71-85 | 08(16.0) | 09(18.0) | |
| >85 | 01(2.0) | 00(0.0) | |
| **Sex** | | | |
| Male | 27(54.0) | 27(54.0) | 1.0 |
| Female | 23(46.0) | 23(46.0) | |
| **Deficit** | | - | - |
| Right Hemiparesis | 25(50.0) | | |
| Left Hemiparesis | 25(50.0) | | |
| **Dyslipidemia** | | | |
| Present | 40(80.0) | 10(20.0) | <0.0001* |
| Absent | 10(20.0) | 40(80.0 | |
| **Hyperuricemia** | | | |
| Present | 22(44.0) | 8(16.0) | 0.002* |
| Absent | 28(56.0) | 42(84.0) | |

** Statistically significant*

**Table 2- Comparison of serum uric acid levels (SUA) between cases and controls**

| | Cases | Controls | p-value |
|---|---|---|---|
| Mean SUA (in mg/dl) | 6.49±2.33 | 5.59±0.97 | *0.01** |
| Range( in mg/dl) | 2.6-12.9 | 2.8-11.9 | |
| Median(in mg/dl) | 7.8 | 6.7 | |

**Statistically significant*

With respect to correlation of serum uric acid levels with clinical and other laboratory parameters among the cases, age(r=0.279), blood urea levels(r=0.608) and serum creatinine levels(r=0.482) were found to be have significant positive correlation with the serum uric acid levels (Table 3).

**Table-3 Correlation of serum uric acid levels with selected clinical and lab parameters among cases (n=50)**

| Parameters | Co-relation coefficient(r) | p-value |
|---|---|---|
| Age (in years) | 0.279 | *0.049** |
| TLC | 0.235 | 0.100 |
| RBS | -0.220 | 0.124 |
| BU | 0.608 | *0.000** |
| SC | 0.482 | *0.000** |
| TC | 0.166 | 0.249 |
| TG | 0.049 | 0.737 |
| HDL | -0.320 | 0.024* |
| LDL | 0.218 | 0.128 |
| VLDL | 0.051 | 0.726 |

** Statistically significant*

With respect to comparison of various lipid profile parameters between cases having hyperuricemia and cases not having hyperuricemia, statistically significant difference(p=0.04) was observed in the prevalence of decreased HDL-C levels between the two groups, implying significant association of Hyperuricemia with Decreased HDL levels. Rest all lipid parameters were found to be similar between the two groups. (Table 4).

**Table 4- Association of Hyperuricemia with individual lipid parameters among the cases (N=50)**

| Lipid Parameters | Hyperuricemia | | | p-value |
|---|---|---|---|---|
| | Present(n=22) | Absent(n=28) | Total | |
| Increased TC (>200 mg/dl) | 8(50.0) | 8(50.0) | 16(100.0) | 0.55 |
| Increased TG (>200 mg/dl) | 6(75.0) | 2(25.0) | 8(100.0) | 0.05 |
| Decreased HDL (<40 mg/dl) | 14(58.3) | 10(41.6) | 24(100.0) | *0.04** |
| Increased LDL (>190 mg/dl) | 2(66.6) | 1(33.4) | 3(100.0) | 0.41 |
| Increased VLDL (>30mg/dl) | 7(41.1) | 10(58.8) | 17(100.0) | 0.77 |

**Statistically significant*

Comparing the various lipid profile parameters between the cases with controls, cases were having significantly higher proportion of increased TG, Increased LDL and Increased VLDL compared to the controls (Table 5).

**Table 5- Comparison of individual lipid parameters between the Cases and the Controls**

| Lipid parameters | Cases (N=50) | | Controls (N=50) | | p-value |
|---|---|---|---|---|---|
| | Present N (%) | Absent N (%) | Present N (%) | Absent N (%) | |
| Increased TC | 16(32.0) | 34(68.0) | 15(30.0) | 35(70.0) | 0.82 |
| Increased TG | 8(16.0) | 42(84.0) | 2(4.0) | 48(96.0) | *0.04** |
| Decreased HDL | 24(48.0) | 26(52.0) | 24(48.0) | 26(52.0) | 1.00 |
| Increased LDL | 03(6.0) | 47(94.0) | 0.0(0.0) | 50(50.0) | *0.001** |
| Increased VLDL | 17(34.0) | 33(46.0) | 4(8.0) | 46(92.0) | *0.001** |

* *Statistically significant*

# Discussion

Stroke continues to be a major public health problem globally. Stroke is frequent, recurring and more frequently disabling than being fatal. Although some risk factors and determinants of stroke such as age, gender, race, ethnicity, and heredity are non-modifiable, there are many modifiable risk factors. Controlling the modifiable factors such as lipid levels and serum uric acid levels may reduce the disease burden. [27]

In our study, fifty patients of ischemic stroke were included out of which 27(54.0%) were males and 23 (46.0%) were females. Similarly, fifty age and sex-matched healthy controls were also included. Mean age of the cases was 60.46±12.30 years ranging from 29 to 86 years whereas mean age of the controls was 60.21±12.12 years ranging from 29 to 81 years. Most of the cases in our study were in the age-group of 56-70 years (38.0%) followed by the age-group of 41-55 years (36.0%). Females cases have significantly higher mean age compared to males(p=0.02). Right sided Hemiparesis was found in 50% of the cases and remaining 50% were having left sided Hemiparesis.

A similar study by Mehrpour et al. [28] from Iran was done in 55 patients with acute ischaemic stroke of which, 30(63.6%) were males and rest 25(36.4%) were females. The mean age of the patients was 67.1±14.3 years somewhat higher than mean age of our cases. In a case control study by Dudhatra et al. [29], the mean age of the cases was 60.56±13.53 years and of control was 57.56±13.06 years and slight male preponderance was observed in both cases and controls similar to our findings. In the case control study by Bhadra et al. [30] conducted among 50 males with acute stroke and 50 age-matched healthy controls at PGIMS, Rohtak, Haryana, North India the mean age of the cases and controls were 59.28±12.31 and 59.88 ±12.06 years respectively similar to mean age of our study participants. In another case control study to assess role of serum uric acid in ischemic stroke by Khalil et al. [31] from Bangladesh, a total of 338 participants were recruited, of which 169 were cases and 169 were controls. Around 60 percent respondents of both case and control groups were males similar to our study population. In the study by Biyani VV et al. [32], 100 patients of first ever lifetime acute ischemic stroke were studied among which 68(68.0%) were males and 32(32.0%) females showing male preponderance. In a recent study by Arora et al. [33] from South India to assess serum uric acid levels and serum lipid levels in patients with ischemic cerebro-vascular accidents, a total of 60 patients were included out of which 43 (71.7%) were males and 17 (28.3%) were females and the mean age of the patients was 63.2 ±14.8 years similar to our case population.

In our study, the mean serum uric acid level of the cases was 6.49±-2.36 mg/dL whereas mean serum uric acid level of the controls was 5.59±0.98 mg/dL, the difference being statistically significant(p=0.01). Similarly, 22(44.0%) out of the 50 cases were hyperuricemic whereas only 8(16.0%) out of the 50 controls were hyperuricemic, this difference in prevalence being statistically significant too(p=0.002). With respect to correlation of serum uric acid levels with clinical and other laboratory parameters, age(r=0.279), Blood

urea levels(r=0.608) and Serum creatinine levels(r=0.482) were found to be have significant positive correlation with serum uric acid.

In the study by Mehrpour et al. [28], the mean serum uric acid level of the patients was 5.94±1.70 mg/dL and 47.3% of the patients were hyperuricemic in line with our study findings. In the study by Dudhtara et al. [29], the mean blood uric acid level of cases was 4.98±1.45 mg/dL and that of controls was 4.36±1.45 mg/dl, the difference being statistically significant (p=0.035). Similarly, in the study by Bhadra et al. [30] the mean blood uric acid level of cases (5.68±1.94 mg/dL) was significantly higher than mean serum uric acid level of controls (3.72±0.96 mg/dL). In the study by Khalil et al. [31], the mean blood uric acid level of cases was 6.03±1.84 mg/dL and that of controls was 4.34±1.60 mg/dL, the difference being statistically highly significant(p=0.000) similar to our findings.

In the study by Biyani VV et al. [32], 49% of the patients of acute ischemic stroke had serum uric acid levels more than 8mg/dL similar to our finding of 44% patients having hyperuricemia. Similar results were also observed in the studies by Millinois et al. [34] and Patil et al. [35]. However, in the study by Arora et al. [33], mean serum uric acid levels of the patients was 5.5 ± 1.7 mg/dL, and 18 patients (30%) were hyperuricemic, both parameters somewhat lower than that found in our study.

In our study, dyslipidaemia was found in 40 (80.0%) cases and only 10(20%) controls(p<0.0001). A statistically significant inverse correlation(p=0.04) of serum uric acid levels with HDL-C was found in the case group. With regard to association of hyperuricemia with deranged lipid parameters, Increased TG levels were seen in 8(16.0%) cases compared to 2(0.0%) controls, (p=0.04). Similarly, Increased LDL-C levels were found in 3(6.0%) cases compared to 0(0.0%) (p=0.001). Finally, Increased VLDL-C levels were observed in 17(38.0%) cases compared to 4(8.0%) among controls (p<0.0001).

In the study by Mehrpour et al. [28] Hyperuricemia was found to be associated with increase in Triglycerides and LDL-C levels. Bhadra J et al. [29] found statistically significant positive correlation of serum uric acid levels with serum TG and VLDL-C levels and an inverse correlation with HDL-C, both among cases and controls. Khalil et al. [31] found no significant difference in serum uric acid levels with or without dyslipidaemia among the ischemic stroke patients. The study by Arora et al. [33] found dyslipidaemia to be seen among 81% of the patients with ischemic stroke similar to our findings. The correlation between serum uric acid levels of the patients and serum TC, TG, LDL and VLDL levels and HDL was found to be statistically non-significant in contrast to our finding of statistically significant inverse correlation between serum uric acid and HDL levels. In the study by Baluch U et al. [36], only 19% patients had dyslipidaemia, 18% had low HDL levels while High LDL, Total Cholesterol and Triglyceride levels were observed in 26%, 24% and 32% respectively. Albucher J.F. et al. [37] concluded in their study that low HDL cholesterol was the only serum lipid index to be associated with increased risk of stroke whereas Samah D et al. [38] found a significant positive correlation of serum uric acid levels with serum TC, TG, LDL, and negative correlation with serum HDL levels, also observed in our study.

*Strengths & Limitations*

This study was based on data collected from a department of a single tertiary care teaching Institute in Haryana, North India making it less representative for the entire population of the region or the country. Besides, population recruited in the control group was also taken from hospital OPD patients that might lead to selection bias. Although cases of this study were directly supervised for overnight fasting before collecting blood samples, supervision of the controls was not possible as they were taken from the out-patient department. Some other variables known to influence SUA level such as body mass index (BMI) and metabolic disorders were not addressed in the study. However, despite these limitations, this study provides a unique perspective since it has analyzed the role of SUA in acute ischemic stroke while considering some well-established cardiovascular risk factors.

# Conclusion

Elevated SUA level is significantly associated with the occurrence of acute ischemic stroke among the patients from Northern India. Presence of Hyperuricemia among the cases was also found to be significantly associated with decreased serum HDL levels, a cardioprotective cholesterol. In light of study findings, Elevated serum uric acid levels or Hyperuricemia may be considered an independent risk factor for acute ischemic stroke.

# Declarations

### Declaration of patients' consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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# Figures

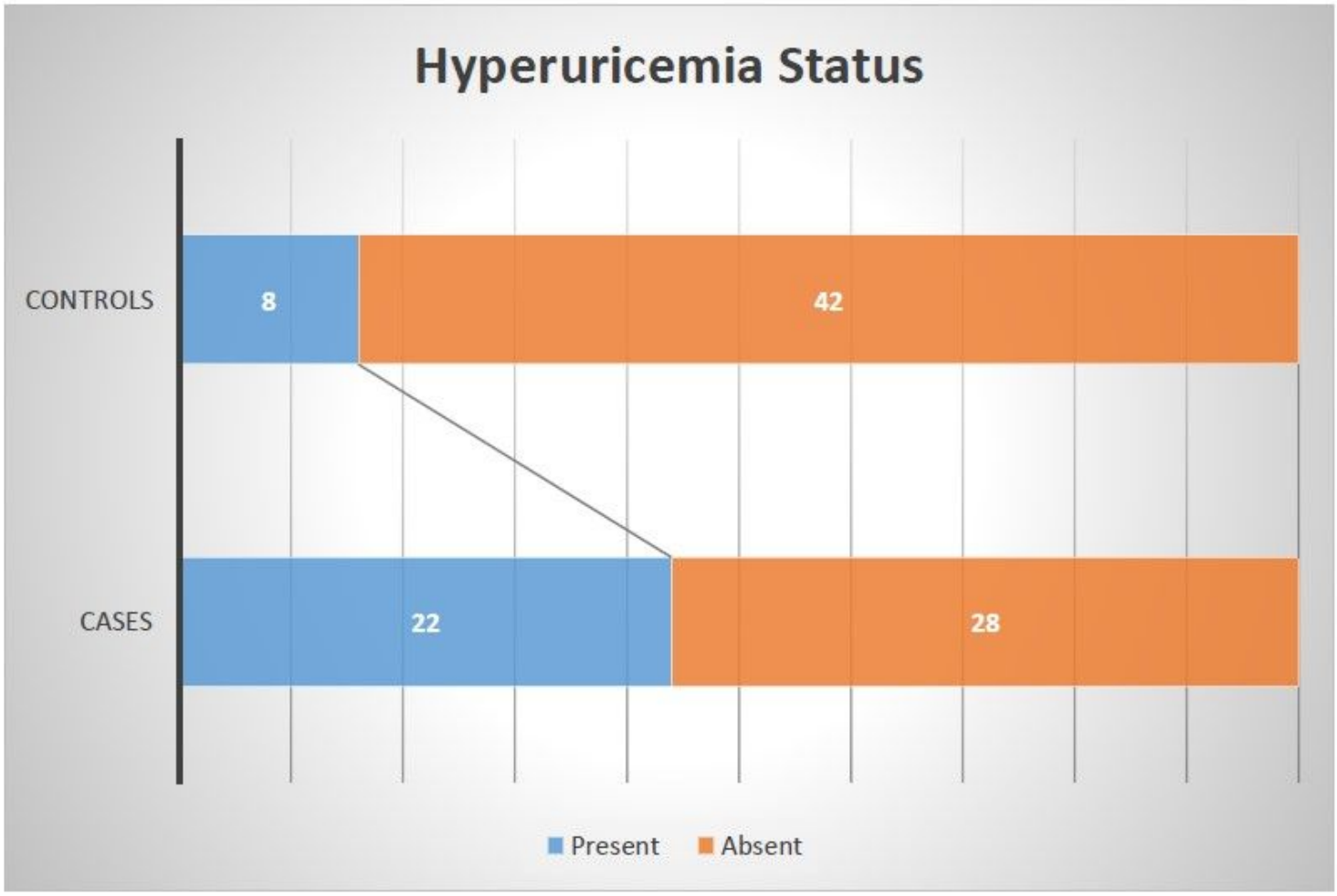


**Figure 1**

Legend not included with this version