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Original Article

Association of Serum gamma-glutamyl transferase with risk factors of Stroke

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ABSTRACT:

Background: Stroke entails a high socioeconomic burden due to increased morbidity and mortality and more commonly affects elderly patients who comprise a continuously increasing proportion of the population in developed countries. Ischemic stroke accounts for about 80% of total stroke events. There are several risk factors of stroke of which diabetes mellitus, hypertension, smoking, high cholesterol, atrial fibrillation, alcohol consumption, obesity, Family history of stroke are most important. **Aim:** To evaluate various risk factors associated with acute stroke patients and correlate them with serum gamma-glutamyl transferase GGT levels in both young and elderly population. **Material and methods:** a total sample of 200 patients were included which were grouped as Group A as case population, comprising of 100 patients with acute stroke and Group B as comtrol, comprising of 100 age and sex matched subjects without obvious cerebrovascular diseases. All were subjected to routine history taking particularly alcohol consumption, use of drugs, smoking, hypertension, diabetes mellitus, dyslipidemia, general physical examination, systemic examination, biochemical tests like Liver function test, Lipid profile, Blood sugar, Blood Urea and Serum Creatinine , serum GGT and lastly neuro-imaging (only for group A). **Results**: In young individuals, Serum GGT levels correlated positively with serum cholesterol, serum triglyceride, Serum HDL, LDL and VLDL. This association in comparison to Serum GGT levels was considered statistically significant. Difference of GGT levels when compared between in hypertensives and non hypertensives between both the groups came to be statistically significant. **Conclusion**: These correlations and findings helps us in focussing on specific interventions to manage blood pressure, smoking, lipid profile and promote physical activity and a healthy diet which could substantially help in reducing the burden of stroke.

Key Words: Acute stroke, risk factors, hypertension, serum GGT.

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INTRODUCTION:

Stroke entails a high socioeconomic burden due to increased morbidity and mortality and more commonly affects elderly patients who comprise a continuously increasing proportion of the population in developed countries. Ischemic stroke accounts for about 80% of total stroke events.[1]

The prevalence of stroke in India shows a huge variation of 147-922/100,000 across diverse community-based studies.[2,3]There are several risk factors of stroke of which diabetes mellitus, hypertension, smoking, high cholesterol, atrial fibrillation, alcohol consumption, obesity, Family history of stroke are most important[4,5.]

Many risk factors are associated with incidence of stroke. Out of all these factors documented in literature, Some risk factors like gender, age and family history cannot be controlled. However, many stroke risk factors which are are lifestyle related like hypertension, smoking, artherscleroses and lipid profile, diabetes, obesity and lack of physical activity can to some extent be controlled. Overall risk increases when multiple risk factors are present.

Serum gamma glutamyl transferase (GGT) is now a days an affordable, highly-sensitive and reliable laboratory test which is frequently used as a hepatobiliary dysfunction and alcohol abuse indicator. Its circulating half-life is seven to 10 days, which is increased in alcohol-associated liver injury because of impaired clearance.[6] In addition, changes in serum GGT levels can be affected by waist circumference and body mass index, hypertension, diabetes, hyperuricemia and genetic factors.[7-11]

Several population based studies have found positive associations of GGT with incidence of cerebrovascular events[12] with proposed mechanism of oxidative stress[13]. Elevated serum GGT levels may be a reflection of high degree of oxidative stress which is known to be associated with atherosclerosis. High level of serum GGT may be found with various atherosclerotic risk factors such as Diabetes Mellitus, Dyslipidemia and

Hypertension independent of alcohol consumption and hepatic dysfunction.[14]

Therefore, this study was aimed to evaluate various risk factors associated with acute stroke patients and correlate them with serum gamma-glutamyltransferase GGT levels in both young and elderly population.

MATERIAL AND METHODS:

This was an observational, cross sectional, comparative hospital based study that was conducted at Guru Nanak Dev Hospital, Amritsar. The study was conducted after approval from Institutional Ethics Committee and written informed consent was taken from all the participants included in the study.

Total 200 patients who met the inclusion and exclusion criterias of the study were taken for the evaluation. Two groups namely group A and group B were formed , Group A which is the study population comprised of 100 Patients admitted in medicine department from Emergency and Medicine outdoor with CT SCAN/MRI with age >18 years, showing acute stroke (first episode). Group B (control group) comprised of 100 age and sex matched subjects without obvious cerebrovascular diseases. Patients who had a past history of stroke, patients with conditions like intrinsic liver disease, alcohol use disorder, congestive cardiac failure etc were excluded from the study. The patients in group A and group B were subjected to routine history taking particularly alcohol consumption, use of drugs, smoking, hypertension, diabetes mellitus, dyslipidemia, general physical examination, systemic examination, biochemical tests like Liver function test, Lipid profile, Blood sugar, Blood Urea and Serum Creatinine , serum GGT and lastly neuro-imaging (only for group A).

RESULTS:

The mean values of demographic and laboratory characteristics of the study population are mentioned in Table 1&2.

TABE 1: MEAN VALUES OF DEMOGRAPHIC CHARACTERISTICS OF THE STUDY POPULATION

CHARACTERISTIC OF POPULATION	GROUP 1 CASE SUBJECTS (N=100)	GROUP 2 CONTROL SUBJECTS (N=100)
AGE (YEARS)	59.48 ± 10.23	59.8 ±9.04
GENDER: MALE FEMALE M:F RATIO	 57 (57%) 43 (43%) 1.3:1	 57 (57%) 43 (43%) 1.3:1
NO. OF DIABETIC PATIENTS NO. OF NON DIABETIC PATIENTS	48 (48%) 52 (52%)	6 (6%) 94 (94%)
NO. OF HYPERTENSIVE PATIENTS	84 (84%)	62 (62%)
SMOKERS	51 (51%)	32 (32%)
SBP (mmHg)	168.98 ±27.78	151.04 ±29.15
DBP (mmHg)	104.32 ±15.9	93.24 ±16.14
PULSE RATE (per min)	83.91 ±12.6	75.57 ±12.7
WAIST CIRCUMFERENCE RATIO	88.82±14.02	77.24±7.45

TABLE 2 : MEAN VALUES OF LABORATORY CHARACTERISTICS OF THE STUDY POPULATION

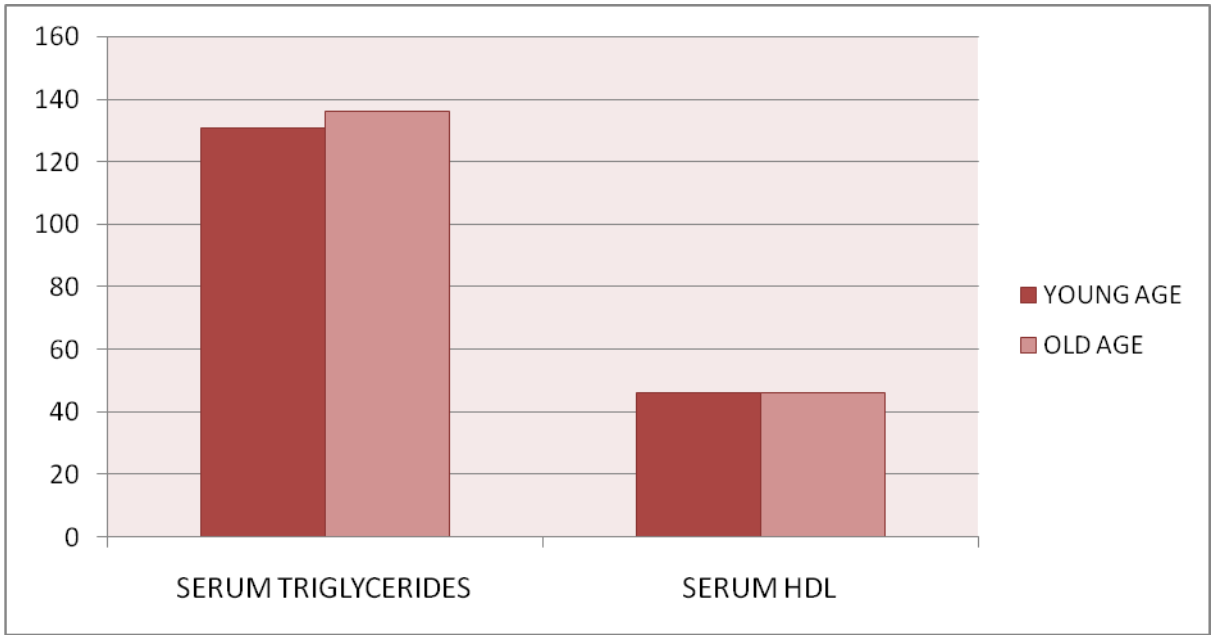
CHARACTERISTIC OF POPULATION	GROUP 1 CASE SUBJECTS (N=100)	GROUP 2 CONTROL SUBJECTS (N=100)
FASTING BLOOD SUGAR	109.61 ±32.0	85.2 ±14.9
POST PRANDIAL BLOOD SUGAR	169.91 ±59.1	115.72 ±29.40
SERUM CHOLESTEROL	189.72 ±40.66	179.18 ±22.13
SERUM TRIGLYCERIDES	140.88 ±61.60	83.01 ±39.24
SERUM HDL	45.68 ±7.67	47.49 ±6.15
LDL	111.98±33.16	113.68±16.05
VLDL	25.91±9.17	16.7±7.55
BLOOD UREA	36.23±13.10	26.17±2.24
SERUM CREATININE	1.28±0.59	0.97±0.28
SERUM URIC ACID	5.68 ±1.18	4.931 ±0.98
SGOT	39.27 ±9.47	32.64 ±3.62
SGPT	28.59 ±4.34	29.14 ±3.78
TOTAL SERUM PROTEIN	6.98 ±0.68	7.36 ±0.46
DIFFERENTIAL SERUM PROTEIN	3.52 ±0.36	3.73 ±0.22
SERUM ALKALINE PHOSPHATASE	108.68 ±43.68	89.76 ±12.17

We also further categorized our study groups according to age as young and old population. Based on previously published studies, stroke in young age was considered in those individuals who were less than fifty years of age while those who aged fifty years or above were considered as old age.[13]

Within group 1, the younger population group comprised of 19 subjects while the older population group comprised of 81 subjects. Gender distribution showed male to female ratio of 2.1:1 and 1.2:1 for younger and adult population respectively.

The difference in Fasting blood sugar and post-prandial blood sugar between both the age groups was also found to be statistically significant (p<0.001). It was observed that difference between both serum triglycerides and serum HDL among both the groups came to be statistically significant (p<0.001) while serum cholesterol levels, VLDL and HDL were found to be statistically non significant (p=0.692) between both age groups. (graph 1)

GRAPH 1: DISTRIBUTION AND COMPARISION OF MEAN VALUES OF SERUM TRIGLYCERIDES AND SERUM HDL IN THE STUDY POPULATION BETWEEN BOTH AGE GROUPS



Biochemical analysis of serum uric acid, blood urea, and serum creatinine was found to be statistically significant (p<0.001) between both groups, but the difference in the SGOT, SGPT levels, total serum proteins, and differential serum proteins, between both the age groups was not statistically significant (p=0.689, 0.489, 0.279, 0.278 respectively). Further it was observed that difference of serum alkaline phosphatise levels between both the age groups came to be statistically signifcant (p<0.001). (graph 2)

Furher when serum GGT levels were compared among hypertensives and non hypertensives within the group 1 population the results were came to be statistically significant. While, on comparision, the difference of GGT levels in diabetics and non dibetics, and between smokers and non smokers came to be statistically non significant. (table 3)

TABLE 3: COMPARISION OF LEVELS OF GGT LEVELS AMONG DIFFERENT PARAMETERS IN CASE GROUP POPULATION

PARAMETER	MEAN LEVEL OF GGT (IU/L)	P VAUE
DIABETES MELLITUS		**P=0.062**
Present (n=)48	**53.04±22.74**	
Absent (n=52)	**50.53±26.34**	
HYPERTENSION		**P<0.001***
Present (n=84)	**56.04±22.19**	
Absent (n=16)	**29.19±24.90**	
SMOKERS		**P=0.07**
Present (n=51)	**55.78±22.19**	
Absent (n=49)	**47.53±22.37**	

Serum GGT levels correlated positively according to univariate analysis with waist circumference ratio (R=0.28), serum cholesterol (R=-0.98), serum triglycerides (R=-0.92) LDL (R=0.94), VLDL (R=0.92) and Serum HDL (Spearman rho, R= 0.53), in the young individuals of case population (group 1). While in old age case population, Serum GGT levels also correlated positively with, Waist circumference ratio (R=0.71), Serum cholesterol (R=-0.11) and serum triglycerides (Spearman rho, R= 0.02; but was inversely correlated with serum HDL (R=-0.07).

TABLE 4: SERUM GGT QUARNTILES AND NUMBER OF FATAL CASES IN BOTH AGE GROUPS OF CASE POPULTION (GROUP 1)

Serum ggt levels QUARANTILES	FATAL CASES YOUNG AGE	FATAL CASES OLDER AGE	P VALUE
1.≤16 IIU/L	-	-	<0.001*
2. 16-21 IIU/L	1	1	
3.22-27 IIU/L	-	1	
4.>27 IIU/L	2	12	

Therefore by normal standards, in young population the association between all the above mentioned variables in comparison to Serum GGT levels were considered as statistically significant, except waist circumference ratio. While this association between Waist circumference ratio was considered statistically significant in old age individuals and rest all the above variables would not be considered statistically significant.

Further when we correlated serum GGT levels with various biochemical markers in the study, it was observed that In young individuals of case population, Serum GGT levels correlated positively according to univariate analysis with serum uric acid (R=0.32), Blood urea (R=0.07), serum creatinine (R=0.23), SGPT (R=-0.17), SGOT (R= 0.12), total serum protein (r=0.12), differential serum protein (R=0.12) and with serum alkaline phosphatase (R= 0.74) . But only the association between serum alkaline phosphatase in comparison to Serum GGT levels was considered as statistically significant.

In older individuals of case population, Serum GGT levels correlated positively with all the variables i.e with serum uric acid (R=-0.11, P=0.29), blood urea (R=0.77), serum creatinine (0.81), SGOT (R= 0.13 ; p=0.23), SGPT (R=-0.09, P=0.37), with total serum protein (R=0.04, p=0.68) , with differential serum protein (R=0.02, P=0.84) and with serum alkaline phosphatase (R= 0.15, P=0.15). But it was observed that correlation with only blood urea and serum creatinine were found to be statistically significant.

Next it was observed that a total of 3 fatal cases were observed in young population of our case population whereas 14 cases were in older age grouop. Further according to the type of major stroke event it was seen that intracerebral haemorrhage was the cause of fatality in 2 cases in young age group and 11 cases in old age group individuals where as subarachanoid haemorrhage was the cause of fatality in 1 cases in young age group and 2 cases in old age group individuals and ischaemic infarct was the cause of fatality in only 1 case in older population only.

On comparision of fatal cases in both young and older population in the control group distributed according to the different serum GGT quarantiles, It was observed that the difference between fatal cases in the highest quarantile of GGT Levels (>27 IIU/L) between both the groups showed a statistically significant result (p<0.001).(table 4)

DISCUSSION:

In the present study it was Stroke patients (group1) have higher incidence of number of diabetic cases (48%), hypertensive cases (84%) and smokers (51%). In accordance to our study Korantzopoulos P et al (2009)[15] also reported prevalence of smoking habits, diabetes, and hypertension to be similar in stroke patients and controls.

On comparison the systolic blood pressure, diastolic blood pressure, pulse rate, waist circumference ratio, fasting blood sugar and Post-prandial blood sugar was higher in stroke patients and the difference between both the groups came to be statistically significant (p<0.001). Also, it was observed that for the stroke patients had higher levels of serum cholesterol, serum triglycerides, LDL and VLDL, whereas, serum HDL levels were higher in control population. Korantzopoulos P et al (2009)[15] reported that Serum total cholesterol, LDL-cholesterol and apolipoprotein B levels were similar in both stroke and control population, whereas stroke patients had higher values of TG and lipoprotein (a) and lower concentrations of HDL-cholesterol and apolipoprotein.

On Biochemical analysis for the same group mean blood urea was 36.23±13.10, mean serum uric acid was 5.68 ±1.18, mean serum creatinine was 1.28±0.59, mean SGOT was 39.27 ±9.47 and mean SGPT was 28.59 ±4.34 Further, it was observed that the total serum proteins, differential serum proteins, and serum alkaline phosphatise levels were 6.98 ±0.68, 3.52 ±0.36, 108.68 ±43.68 respectively.

In the present study the study population was further categorised according to age as younger (<50 years of age) and older population (>50 years of age). On comparison between both the age groups, the difference in the waist circumference ratio, systolic blood pressure, diastolic blood pressure, Fasting blood sugar, Post-prandial blood sugar, serum triglycerides, serum HDL, blood urea, serum uric acid, serum creatinine and serum alkaline phosphatise levels were found to be statistically significant. Whereas, parameters like serum cholesterol, LDL, VLDL, SGOT, SGPT levels, total serum proteins, and differential serum proteins, between both the age groups was not statistically significant.

On comparison, the difference of GGT levels when compared between in hypertensives and non hypertensives between both the groups came to be statistically significant. While between diabetics and non diabetics, it is observed that the levels were higher in diabetics but difference in values between both the groups is statistically not significant. Hypothetically, diabetic status and elevated GGT may have a cumulative or additive action exacerbating the impact of these conditions and strengthening the association with CVD and mortality. Lee DH, et al (2006)[16] also suggested that the association of GGT with mortality may be stronger in patients with diabetes. Ndrepepa G (2016)[17] also reported

cohort studies with type 2 diabetes showing significant association of GGT levels with mortality in these patients. On univariate regression analysis, Serum GGT levels were correlated positively with serum cholesterol, serum triglycerides and Serum HDL, LDL and VLD in the young individuals of case population. By normal standards, this association in comparison to Serum GGT levels was considered statistically significant. Whereas Serum GGT levels though correlated positively with, Serum cholesterol and serum triglycerides in the old individuals of case population and inversely with serum HDL, the association between all the above variables in comparision to Serum GGT levels would not be considered statistically significant. Korantzopoulos P et al (2009)[15] demonstrated that overall GGT levels in stroke patients correlate positively with lipid parameters (LDL-cholesterol, TG), creatinine, uric acid, BMI, serum glucose, smoking and hypertension. On the contrary, there seems to be an inverse correlation with HDL-cholesterol levels. Gurbuzer N (2014)[18] also reported Increased GGT level in the subgroup with hypertension, higher LDL-cholesterol, and triglyceride levels among cases with acute stroke.

In the present study we studied cases with 3 major stroke events namely intracerebral haemorrhage, ischaemic infarct and subarachanoid haemorrhage. Our results show that majority stroke cases in young population were of ischaemic infarcts but all those patients survived while maximum fatal cases were observed in cases of subarachanoid haemorrhage. Whereas in comparison to younger population, older population showed greater number of fatal cases (17.28%) and major fatal events were due to intracerebral haemorrhage.

Jousilahti et al. [19] reported that there was also a significant association between GGT and the risk of intracerebral hemorrhage. The relationships remained statistically significant also after adjustment for other risk factors. D. Ambrosio et al.[20] reported that increased gammaglutamyl transferase levels predict functional impairment in elderly adults after ischemic stroke. Korantzopoulos et al.[15] also found positive correlation between serum gammaglutamyl transferase and acute ischemic nonembolic stroke in the elderly subjects.

CONCLUSION:

Our findings suggest various risk factors associated with of the risk of stroke along with the serum GGT levels as a marker for stroke. We can summarize our findings as follows:

- In young individuals, Serum GGT levels correlated positively with serum cholesterol, serum triglyceride, Serum HDL, LDL and VLDL. This association in comparison to Serum GGT levels was considered statistically significant.
- Whereas in older individuals, Serum GGT levels correlated positively with Serum cholesterol and serum triglycerides; and inversely with serum HDL. By normal standards, the association between the above variables in comparision to Serum GGT levels would not be considered statistically significant.
- Difference of GGT levels when compared between in hypertensives and non hypertensives between both the groups came to be statistically significant.
- Mean GGT levels were observed higher in diabetics than non diabetics, but difference in values between both the groups is statistically not significant.

These correlations and findings helps us in focussing on specific interventions to manage blood pressure, smoking, lipid profile and promote physical activity and a healthy diet which could substantially help in reducing the burden of stroke.

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