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## Original Research Article

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## Association between serum Gamma-Glutamyl Transferase (GGT) level and acute stroke.

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### Abstract

**Background:** In developing countries like India, stroke is one of the leading causes of morbidity and mortality due to high prevalence of risk factors like hypertension, diabetes mellitus, obesity, dyslipidemia, alcohol intake and smoking. Gamma glutamyl transferase (GGT) is an enzyme that plays an important role in synthesis and degradation of glutathione. Several studies suggest the role of GGT in cardiovascular and cerebrovascular diseases. **Aim:** This study was done to study the serum GGT level as a risk factor in acute stroke. **Material and methods:** Two groups that is group A and group B were formed among the total 200 patients that were considered for evaluation. Group A comprised of 100 patients with acute stroke. Group B comprised of 100 age and sex matched subjects without obvious cerebrovascular diseases.

**Results:** The mean serum GGT level in group A was 51.74 U/L while in group B it was 17.99 U/L and this difference in the GGT levels between both the groups was statistically significant.

**Conclusion:** Higher GGT levels in stroke patients relative to the control group reinforce the relationship of GGT with inflammation and oxidative stress.

**Keywords:** Gamma-Glutamyl Transferase, Acute stroke

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### Background

Stroke is defined as a rapid onset of focal or global cerebral deficit, lasting for more than 24 hours (unless interrupted by death or surgery) with no apparent cause other than a vascular one. The pathological background for stroke may either be ischemic or hemorrhagic disturbances of the cerebral blood circulation.<sup>1</sup>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. The prevalence of stroke in India shows a huge variation of 147-922/1,00,000 in several community-based studies.<sup>2,3</sup>There are several risk factors of stroke of which diabetes mellitus, hypertension, smoking, dyslipidemia, atrial fibrillation, alcohol consumption, obesity, family history of stroke are most important.<sup>4,5</sup>

Gamma Glutamyl Transferase (GGT) is an enzyme which was discovered by Hanes in 1951.<sup>6</sup>In most cases, serum GGT levels are examined for the diagnosis of liver, gallbladder and biliary tract diseases especially in alcoholic liver disease.<sup>7,8</sup> GGT is expressed not only in liver and kidney but also in cerebrovascular endothelium, pericytes and other cell types. GGT is released by atherosclerotic plaques in damaged cerebral vascular endothelial cells; this finding may explain the predictive value of GGT in cerebrovascular diseases.<sup>9</sup> Several population based studies have found positive association of GGT with incidence of cerebrovascular events with proposed mechanism of oxidative stress.<sup>10,11</sup> Numerous studies have found that GGT is not just a marker of alcohol consumption but is an independent predictor of many conditions including cardiovascular diseases, diabetes mellitus, inflammation and possibly underlying oxidative stress.<sup>12-19</sup> This study focussed on evaluating the level of serum GGT in acute stroke in both young and elderly population.

## Materials and Methods

The study was an observational study that was conducted at Guru Nanak Dev Hospital, Amritsar. Total 200 patients who met the inclusion and exclusion criteria of the study were taken for the evaluation. Two groups that is group A and group B were formed among the total patients that were considered for evaluation. Group A comprised of 100 patients with acute stroke. Group B comprised of 100 age and sex matched subjects without obvious cerebrovascular diseases. Patients more than 18 years of age who presented with first episode of acute stroke and those who presented with health ailments in which there was no elevation of serum GGT were included in

group A and group B respectively. Patients who had a past history of stroke, intrinsic liver disease, alcohol use disorder, congestive cardiac failure were excluded from the study. The patients in group A and group B were subjected to routine history taking, general physical examination, systemic examination, biochemical tests and neuroimaging (only for group A). Serum GGT was estimated using carboxy substrate method. Normal value of serum GGT for males is 10-50 U/L and for females is 07-35 U/L.<sup>20</sup> 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.<sup>21</sup> The study was conducted after approval from institutional thesis and ethical committee.

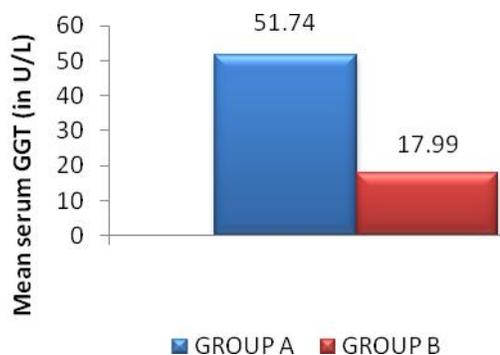
## Results

It was seen that the mean age in years in group A and group B was almost similar that is  $59.48 \pm 10.23$  years and  $59.8 \pm 9.04$  respectively. Even when comparison was made between younger and older population between the two groups, it was also similar such that there were 19 younger age individuals in group A as compared to 18 younger age individuals in group B and 81 older age individuals in group A as compared to 82 older age individuals in group B.

When gender distribution was compared among both the groups, it was seen that both groups had an almost equal distribution of males and females with slight predominance of males in both the groups. There were 57 males in group A in comparison to 53 males in group B and 43 females in group A in comparison to 47 females in group B.

**Table 1. Distribution and comparison of mean values of serum GGT levels within the study population between two groups**

Characteristic of population	Group A (n=100)	Group B (n=100)	p value
Mean serum GGT $\pm$ standard deviation (in units/litre)	$51.74 \pm 22.19$	$17.99 \pm 3.8$	< 0.001*

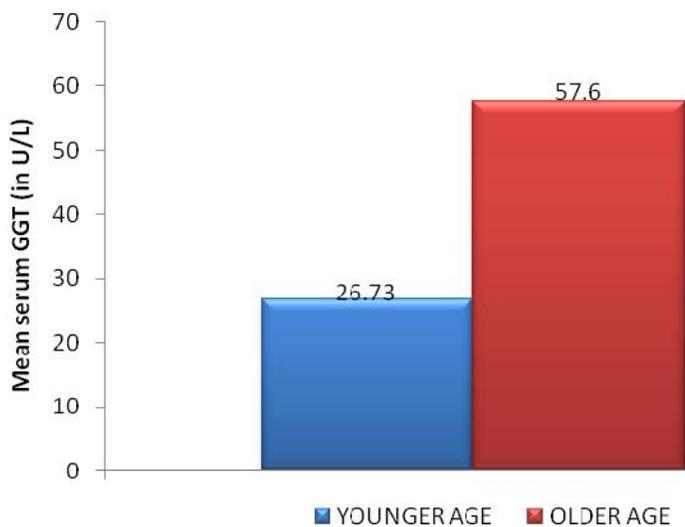


The mean serum GGT level in group A was 51.74 U/L while in group B it was 17.99 U/L. This difference in

the GGT levels between both the groups was statistically significant ( $p < 0.05$ ).

**Table 2. Distribution and comparison of mean values of serum GGT levels within group A**

Characteristic of population	Younger age group (n=19)	Older age group (n=81)	p value
Mean serum GGT $\pm$ standard deviation (in U/L)	26.73 $\pm$ 29.76	57.60 $\pm$ 18.31	< 0.001*

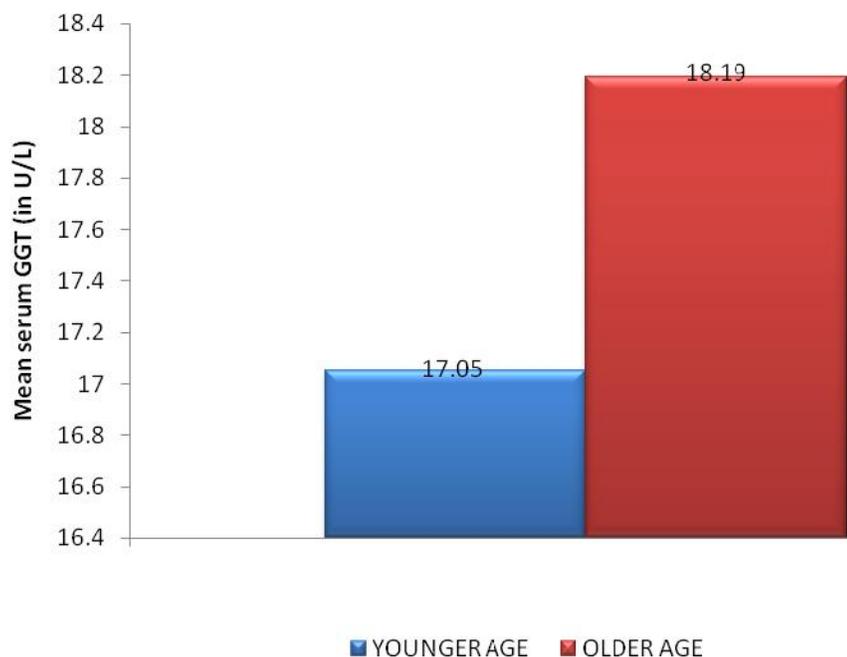


The mean serum GGT levels in young age group was 26.73 U/L while in older age group it was 57.60 U/L.

This difference in the GGT levels between both the groups was statistically significant ( $p < 0.001$ ).

**Table 3. Distribution and comparison of mean values of serum GGT levels within group B**

Characteristic of population	Younger age group (n=18)	Older age group (n=82)	p value
Mean serum GGT $\pm$ standard deviation (in U/L)	17.05 $\pm$ 3.74	18.19 $\pm$ 3.82	0.257

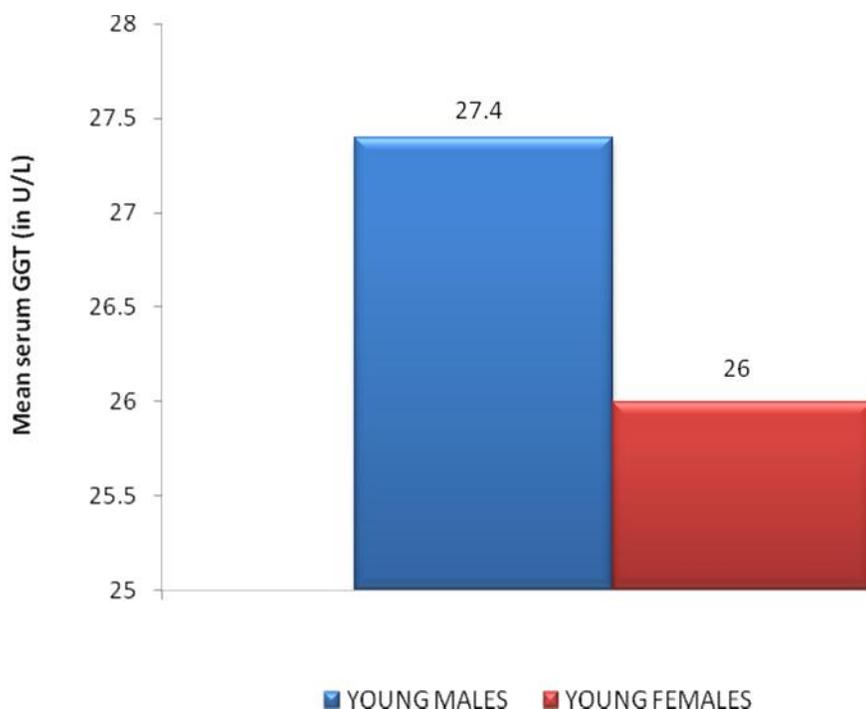


The mean serum GGT levels in young age group was 17.05 U/L while in older age group it was 18.19 U/L.

This difference in the GGT levels between both the groups was statistically not significant.

**Table 4. Gender distribution and comparison of mean values of serum GGT levels in younger population within group A**

Characteristic of population	Younger males (n=10)	Younger females (n=9)	p value
Mean serum GGT ± standard deviation (in U/L)	27.4 ± 6.50	26 ± 8.12	0.269

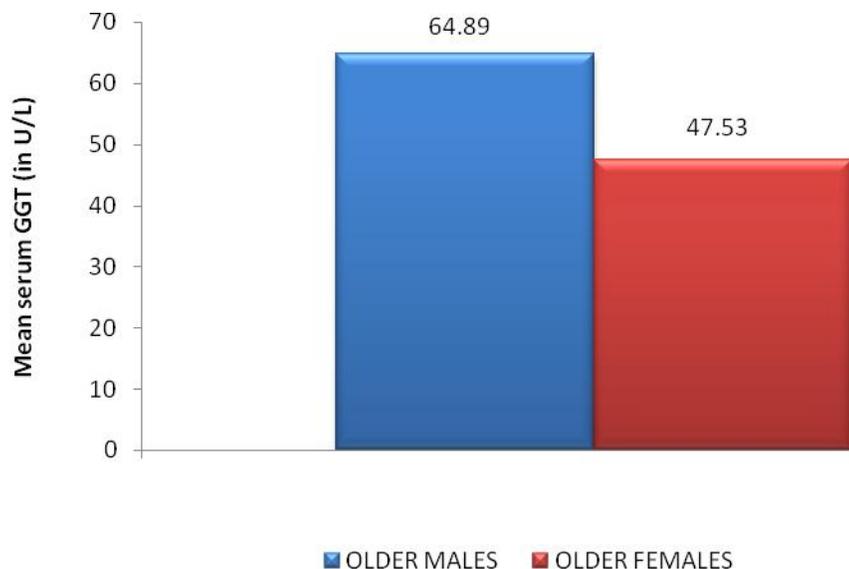


The mean serum GGT levels in group A in young males was 27.4 U/L while in young females it was 26

U/L. This difference in the GGT levels between both the groups was statistically not significant.

**Table 5. Gender distribution and comparison of mean values of serum GGT levels in older population within group A**

Characteristic of population	Older males (n=47)	Older females (n=34)	p value
Mean serum GGT ± standard deviation (in U/L)	64.89 ± 21.67	47.53 ± 13.04	<0.001*



The mean serum GGT levels in group A in older males was 64.89 U/L while in older females it was 47.53 U/L. This difference in the GGT levels between both the groups was statistically significant as p value is less than 0.05.

**Discussion**

In our study, the mean age in years in group A and group B was almost similar i.e 59.48 ± 10.23 years and 59.8 ± 9.04 years respectively. Even when comparison was made between younger and older population between the two groups, it was also similar such that there were 19 younger age individuals in group A as compared to 18 younger age individuals in group B and 81 older age individuals in group A as compared to 82 older age individuals in group B.

When gender distribution was compared among both the groups, it was seen that both groups had an almost equal distribution of males and females with slight predominance of males in both the groups. There were 57 males in group A in comparison to 53 males in group B and 43 females in group A in comparison to 47 females in group B.

In concordance with our study, Gurbuzer N<sup>22</sup> also reported that a significant difference was not found between the groups regarding their mean ages and gender distribution. Bots et al.<sup>23</sup> reported a mean age of stroke patients in their study as 65.9 ± 11.3 years, Ruttman et al.<sup>24</sup> reported a mean age of 41.8 ± 14.7 years in men and 42.0 ± 15.9 years in women, Wannamethee et al.<sup>25</sup> reported a mean age of 50 years.

It was observed that mean serum GGT level in group A was 51.74 U/L while in group B it was 17.99 U/L. This difference in the GGT levels between both the groups was statistically significant. Similarly, in support to our study Korantzopoulos P et al.<sup>26</sup> also reported that GGT levels were significantly higher in stroke patients compared to controls. Gurbuzer N<sup>22</sup> also reported that mean GGT levels in the acute ischemic stroke group was found to be significantly higher relative to the control group. From another study conducted in Japanese men and women, it was concluded that GGT is associated with increased risk of all strokes and ischemic strokes for Japanese women especially in teetotalers.<sup>27</sup>

Meisinger C et al. reported the association of GGT activity with the risk for acute ischemic events that was investigated in the population based MONICA (Monitoring trends and determinants on cardiovascular diseases), Augsburg survey conducted between October 1984 and June 1985. The study included 1,878 healthy men aged 25–64 years who were free of cardiovascular disease at baseline, until it was seen a total of 150 acute ischemic events of new onset occurred. The study strongly suggested that GGT elevation predicts the occurrence of acute ischemic events in apparently healthy men.<sup>28</sup> A recent meta-analysis conducted in 5707 cases and 9,26,497 participants by Xiao-Wei Zhang et al. concluded that an elevated serum GGT levels were significantly associated with stroke independent of alcohol consumption.<sup>29</sup>

It was seen that mean serum GGT levels in patients with stroke in younger age group was 26.73 U/L while in older age group it was 57.60 U/L. This difference in the GGT levels was statistically significant. This is in accordance with Rotterdam study where it was seen that age is a non modifiable risk factor for stroke and the risk for stroke increases with increasing age, thus resulting in higher prevalence of stroke in older population in comparison to younger population. It was also observed that the number of diabetics and hypertensive individuals were more in older age as compared to younger age as diabetes mellitus and hypertension are risk factors for stroke. Higher prevalence of these risk factors in older age can also account for higher incidence of stroke in older age.<sup>30</sup> Older population showed serum GGT levels higher than the younger population. This observation is similar to the earlier finding by Mijovic V et al.<sup>31</sup> where it was seen that serum GGT level is higher in older age group. Study by Puukka et al.<sup>32</sup> also showed that serum GGT activity increases with increasing age. Korantzopoulos P et al. conducted a study with an aim to determine whether GGT levels are associated with acute ischemic stroke in a case-control study of elderly subjects. They reported that there are positive associations between serum GGT and first ischemic stroke in individuals 70 years of age independent of established risk factors for cardiovascular disease and concurrent metabolic abnormalities.<sup>26</sup>

It was seen that mean serum GGT levels in group A in young males was 27.4 U/L while in young females it was 26 U/L. This difference in the GGT levels between both the groups was statistically not significant. It was seen that the mean serum GGT

levels in group A in older males was 64.89 U/L while in older females it was 47.53 U/L. This difference in the GGT levels between both the groups was statistically significant.

This difference in the two observations could be due to huge difference in sample size that included 19 younger and 81 older subjects in group A. Overall it was seen that mean serum GGT level was higher in males as compared to females with difference being significant in older subjects. This is similar to study by Mijovic V et al.<sup>31</sup> in which GGT levels were higher in males in comparison to females. This difference may also be probably due to increased incidence of smoking in males than females and smoking can increase oxidative stress.

However, this observation does not support the result of Japanese study by Yuji Shimizu et al.<sup>33</sup> which concluded that serum GGT is higher in females in comparison to males. This difference in result may be due to different socioeconomic status and proportion of smoking in both these studies. In our study most of the male patients were smokers and all female patients were nonsmokers.

## Conclusion

GGT has been underestimated for being just a surrogate marker of liver diseases and our results validate the correlation between GGT and stroke. The major causes of stroke are atherosclerosis and cardio-embolism and both these conditions could be related to an increased systemic burden of oxidative stress. Therefore higher GGT levels in stroke patients relative to the control group reinforce the relationship of GGT with inflammation and oxidative stress. Thus we can say that although GGT may serve as a cheap, convenient and effective biomarker to predict the occurrence of stroke, it should be interpreted cautiously as increased serum GGT might reflect an elevated oxidative stress that is only transient and has occurred only at the onset of stroke. Therefore to overcome this problem more prospective studies are needed. Hence continuous interest and further researches on GGT are necessary.

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**Conflicts of interest:** There are no conflicts of interest.

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