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A Case Control Study of Plasma Homocysteine Levels in Ischaemic Stroke Patients Among Diabetics and Non-Diabetics Versus Controls

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Abstract

Cerebrovascular disease designates any abnormality of the brain resulting from a pathologic process of the blood vessels.In India, based on a single population based study, the two year prevalence and annual incidence rate are 84 and 13 per 100,000 population, which, when compared with figures quoted from western studies, are much less. A few Indian studies point out that 9.2% to 30% of neurological admissions are patients suffering from a stroke.

BACKGROUND: Increased plasma levels Homocysteine is now considering as individual risk factors for cerebrovascular disease, myocardial infarction, and peripheral arterial occlusive disease. Hyperhomocysteinemia not only accelerates atherosclerosis but also by various mechanisms can increase the incidence of cerebrovascular disease.

The present study is to measure the plasma homocysteine levels in patients presenting with ischaemic strokes and correlate with the levels in diabetics and non-diabetics along with age, Body mass Index(BMI) and sex-matched controls.

There is growing evidence that high homocysteine levels contribute to the pathogenesis of ischaemic stroke. Homocysteine is believed to cause atherogenesis and thrombogenesis via endothelial damage, vascular smooth muscle proliferation, and coagulation abnormalities.

MATERIAL AND METHODS: It was an Observational study (case-control) carried out for a period of 3 years between 2017 -2020 on 50 patients (cases) admitted in the Medicine department, King George Hospital, Visakhapatnam. About 50 asymptomatic controls were taken. The mean values are obtained and compared with controls and evaluated the risk comparison.

RESULTS: High homocysteine levels are associated with increased risk of cerebrovascular disease. The present study has shown an elevation of Homocysteine levels > 10 µmol/L in 89%of patients aged above 45 years.

Keywords: Hyper homo cystenemia, ischemic stroke, Atherosclerosis, Diabetes Mellitus, Age.

INTRODUCTION

Cerebrovascular disease designates any abnormality of the brain resulting from a pathologic process of the blood vessels. The pathologic process may result in ischaemia of the blood vessels resulting in infraction of the brain.

Stroke of all types ranks third as a cause of death, and this is the leading cause of disability in adults. Ischaemic events account for approximately 80% of all strokes.

The incidence in the UK is approximately 2 per 1000 population per year, and about 100,000 patients have a first stroke every year, one every 5 minutes.

In the United States every year, there are approximately 500,000 cases of stroke, roughly 400,000 infractions, and 100,000 hemorrhages.

In India, based on a single population-based study, the two-year prevalence and annual incidence rate are 84 and 13 per 100,000 population, which, when compared with figures quoted from western studies, are much less .[12]

HOSPITAL DATA[2]

Based on many retrospectives and a few prospective studies, cardiovascular disease accounts for 0.9% to 4.5% of total medical admissions in India. A few Indian studies point out that 9.2% to 30% of neurological admissions are patients suffering from a stroke.

The figures are much lower than the figures of Fisher et al. from the U.S.A. where about 50% of neurological admissions are patients with cerebrovascular diseases. As pointed out by Wad, if Indian figures were to be calculated only for adult Neurological hospital admissions excluding the pediatric age group, there might come closer to those mentioned by Fisher et.al. This contention, however, is not held by Venkataraman et al., who state that Cerebrovascular disease constitutes 18.8% of all admissions to the Neurological services of AIIMS. Socioeconomic factors, dietary and lifestyle behaviors, different patterns of risk factors, and environmental conditions may explain the different incidences of stroke observed in different parts of the world.

Several risk factors that may be classified as modifiable and unmodifiable increase the risk of ischemic stroke. The modifiable risk factors have very much clinical significance because modification or alteration of these risk factors can decrease the incidence of stroke in the population. The modifiable risk factors of clinical significance are Hypertension, ***Diabetes mellitus***, Dyslipidemia, Cigarette Smoking, Alcohol consumption, increased fibrinogen, elevated Homocysteine, obesity, etc. Increased plasma levels Homocysteine is now considering as individual risk factors for cerebrovascular disease, myocardial infarction, and peripheral arterial occlusive disease. Hyperhomocysteinemia not only accelerates atherosclerosis but also by various mechanisms can increase the incidence of cerebrovascular disease.

The present study is to measure the plasma homocysteine levels in patients presenting with ischemic strokes and correlate with the levels in age and sex-matched controls.

1.AIM AND OBJECTIVES OF STUDY: The present study aims to determine the levels of Homocysteine in patients with Ischemic stroke aged above 45 years with hypertension and diabetes or both and compare it with controls**.**

2.RISK FACTORS [3,7,8] **:** Several risk factors that are classified as modifiable and non-modifiable for ischaemic stroke are :

NON – MODIFIABLE RISK FACTORS FOR ISCHAEMIC STROKE;

Age

Race/ethnicity

Gender

Family history

Genetics

MODIFIABLE RISK FACTORS FOR ISCHAEMIC STROKE;

Diabetes mellitus

Hypertension

Transient ischemic attacks

Cardiac disease / atrial fibrillation

Aortic arch atherosclerosis

Dyslipidemia

Hyperhomocysteinaemia

Cigarette smoking

Alcohol consumption

Obesity

Oral contraceptive and postmenopausal estrogens.

Above all, the Hyperhomocystenaemia is the parameter of interest taken in this study in ischaemic stroke patients among risk factors of diabetics versus non diabetics among cases and controls.

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DIABETES; a review literature:

Diabetes mellitus increases the risk of ischaemic cerebrovascular disease two to four folds compared with the risk in non-diabetics. The mechanisms of stroke secondary to diabetes may be caused by cerebrovascular atherosclerosis, cardiac embolism, or rheological abnormalities. Diabetic persons with retinopathy and autonomic neuropathy appear to be a group at particularly high risk for ischaemic stroke.

Evidence to date suggests that the metabolism of homocysteine is impaired in-patients with Type 2 diabetes mellitus. Hyperhomocysteinemia is associated with macrovascular disease in a significant proportion of patients with Type 2 diabetes mellitus[28]. Hyperglycemia is undoubtedly associated with a poor outcome after stroke, either because the consequences of ischemia are exacerbated in the presence of high blood glucose concentrations, perhaps mediated by excess lactate production. Or because hyperglycemia reflects the stress response, and so the severity of the initial stroke.

Apart from its alterations in a few of the diseases mentioned above, the focus is on homocysteine and it‟s implications in cardiovascular disorders. In addition to it, several other clinical conditions, including neural tube defects, spontaneous abortion, placental abruption, rheumatoid arthritis[29], osteoporosis, and neuropsychiatric disorder[30], have been linked to homocysteine.

HYPER HOMOCYSTEINEMIA: The interest in Homocysteine has burgeoned during the last few years. Homocysteine is now considered a risk factor for several diseases particularly in Cerebrovascular stroke, cardiovascular diseases, and peripheral athero-occlusive diseases.

Homocysteine is a sulfur-containing amino acid that is closely related to the essential amino acid methionine and cysteine. Butz and Duvigneaud first described Homocysteine in 1932. During the last 15 years, it has been documented that moderately elevated homocysteine levels in serum or plasma are a strong and independent risk factor for occlusive arterial disease and venous thrombosis. As many as 50% of patients with stroke and other atherothrombotic diseases have high homocysteine levels.

Elevated plasma Homocysteine levels in Indians;

Elevated plasma homocysteine levels seem to be a feature of South Asian populations. In the SHARE and the UK study[13], the levels of homocysteine in the South Asians /Indians were higher than those found in the other ethnic groups. For example, in the UK study, fasting homocysteine concentrations were 6% higher in the Indian controls than in the Europeans. Several explanations have been put forward to account for this reduced intake of vitamin B_{12} in Indians and the prolonged cooking of vegetables, which has been observed in some Indian households in the UK. It is believed that this later practice may destroy up to 90% of their folate content. However, it is not known whether lowering plasma homocysteine levels, through B vitamin and folate supplementation, helps in the long run. Subclinical renal dysfunction can be another cause of this elevation. Plasma homocysteine levels rise in parallel to serum creatinine as the glomerular filtration rate[17] falls. Diabetes and resultant renal impairment are known to be much more common among Indians[18]. Homocysteine is an Amino acid formed during the metabolism of methionine. The first step in the synthesis of homocysteine is the formation of S-adenosylmethionine (Adeno-meth), an important methyl donor, from methionine. Adeno-meth is then converted to S-adenosyl homocysteine (Adeno-Hcy), which is further hydrolyzed to yield homocysteine and adenosine, depending on whether there is a relative excess or a deficiency of methionine, homocysteine may then enter either transsulfuration or remethylation pathways.

3.MATERIALS AND METHODS:

STUDY DESIGN: Observational study (case-control)

STUDY PERIOD: From Nov 2017-2020

The present study was carried out on 50 patients (cases) admitted in the Medicine department, King George Hospital, Visakhapatnam. About 50 asymptomatic controls were taken. The patients in this study satisfied the following inclusion criteria.

Inclusion criteria;

- All patients should be aged more than 45 years.
- All patients first-ever diagnosed with having Ischaemic stroke were taken into the present study.

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- Patients who are presented with Diabetes.
- Patients who gave valid consent

Exclusion criteria:

Patients with

▪Ischemic stroke of less than 45 yrs of age was excluded

▪Presenting with more than 48 hrs of duration from the onset of ischemic stroke were excluded

▪Patients who are on drugs that modify the result of homocysteine were excluded ….

Cholestyramine, Methotrexate, L-dopa, Niacin, Theophylline, Androgens, Cyclosporines, Fibric acid derivatives, Phenytoin, Carbamazepine.

▪Prior history of Renal failure, Hypothyroidism, SLE, Psoriasis excluded.

Data collection:

Demographic data like gender and age were collected, and the patients (both cases and controls) were interviewed for the relevant history of risk factor of Diabetes.

A thorough general physical examination was conducted, followed by a systemic examination, and the findings were noted.

Investigations;

▪ Fasting blood samples were drawn for following investigations

▪ Fasting blood sugar, Lipid profile (total cholesterol, triglycerides, HDL and LDL)

▪ Plasma Homocysteine levels.

▪ Homocysteine values more than 10 micromol/l were considered as Hyperhomocysteinemia.

▪ Homocysteine values more than 10 micromol/l were considered as Hyperhomocysteinemia.

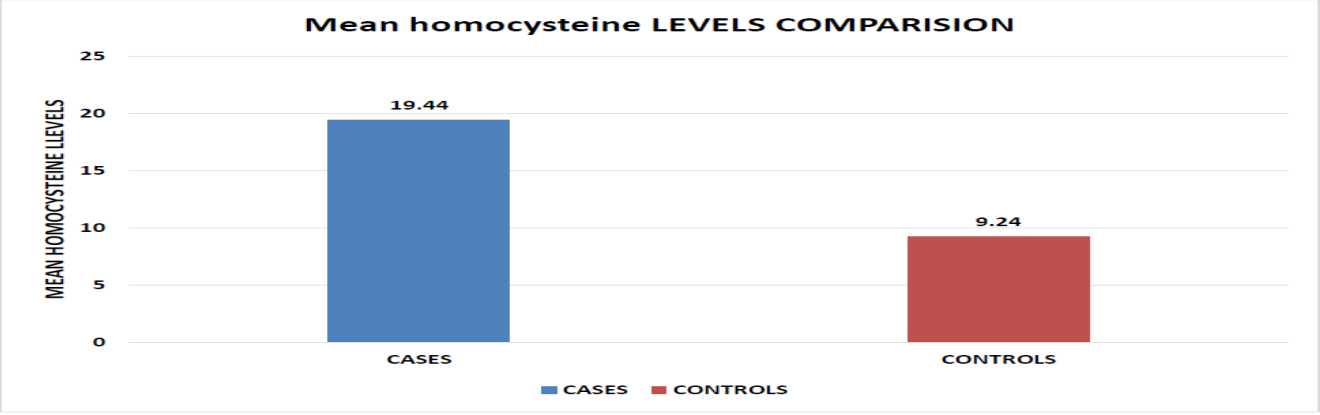
Plasma homocysteine levels: Venous blood (10 ml) collected in EDTA tubes after an overnight fast (14h), using standardized protocol and equipment. Plasma was immediately separated and stored at – 20 C. Plasma samples were analyzed for total homocysteine by the HPCL system.

4. RESULTS:

Table 1. Comparison of mean homocysteine levels between cases & controls

HOMOCYSTEINE	N	MEAN	STANDARD DEVIATION	P value
CASES	50	19.44	5.84	0.001
CONTROLS	50	9.24	1.93	

Figure 1: Comparison of mean homocysteine levels between cases & controls



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The mean homocysteine value among 50 cases is 19.44± 5.84, whereas, in controls, the mean values were 9.24 ± 1.93, the P-value is < 0.001.

TABLE 2: MEAN HOMOCYSTEINE COMPARISON BETWEEN DIABETIC AND NON-DIABETIC

HOMOCYSTEINE	N	MEAN	SD	P value
NON-DIABETIC	36	19.47	5.97	**0.96**
DIABETIC	14	19.39	5.76	

FIG 2; MEAN HOMOCYSTEINE LEVEL COMPARISION BETWEEN DIABETICS AND NON-DIABETICS

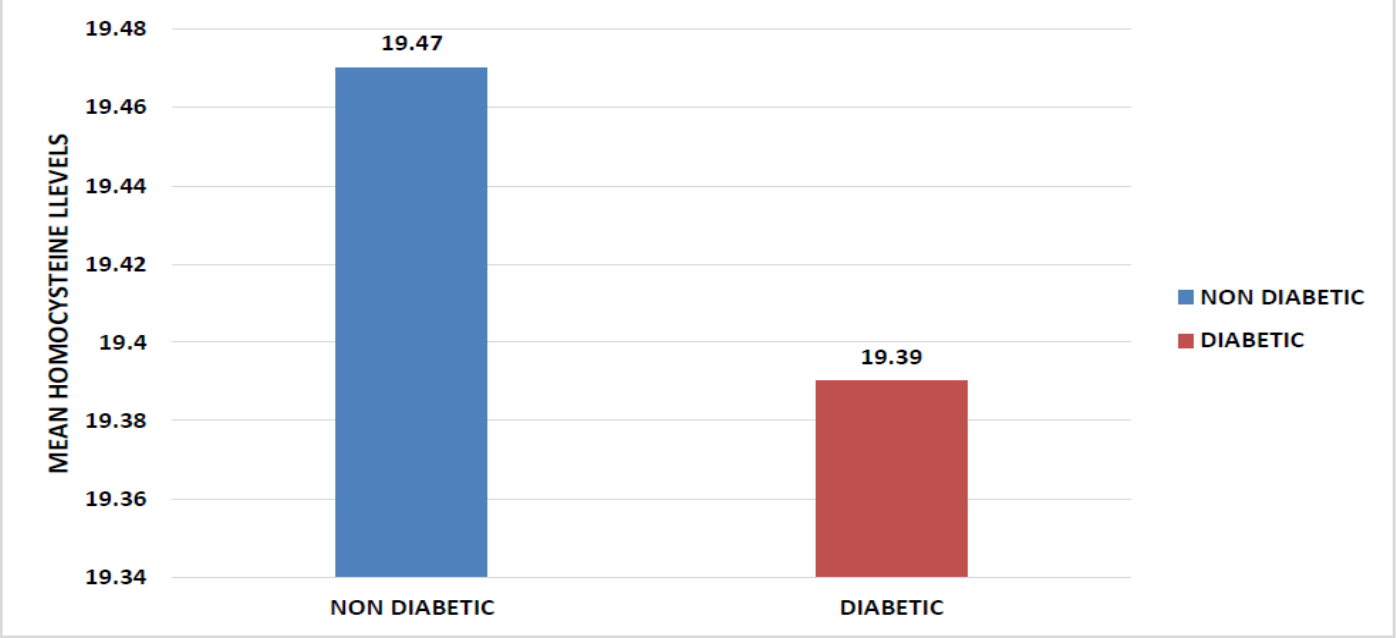

TABLE 3: MEAN BMI(BODY MASS INDEX) COMPARISON BETWEEN CASES AND CONTROLS

BMI	N	MEAN	STANDARD DEVIATION	P VALUE
CASES	50	24.2436	3.20484	**0.33**
CONTROLS	50	23.3370	5.73724	

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Fig 3: Mean BMI comparision

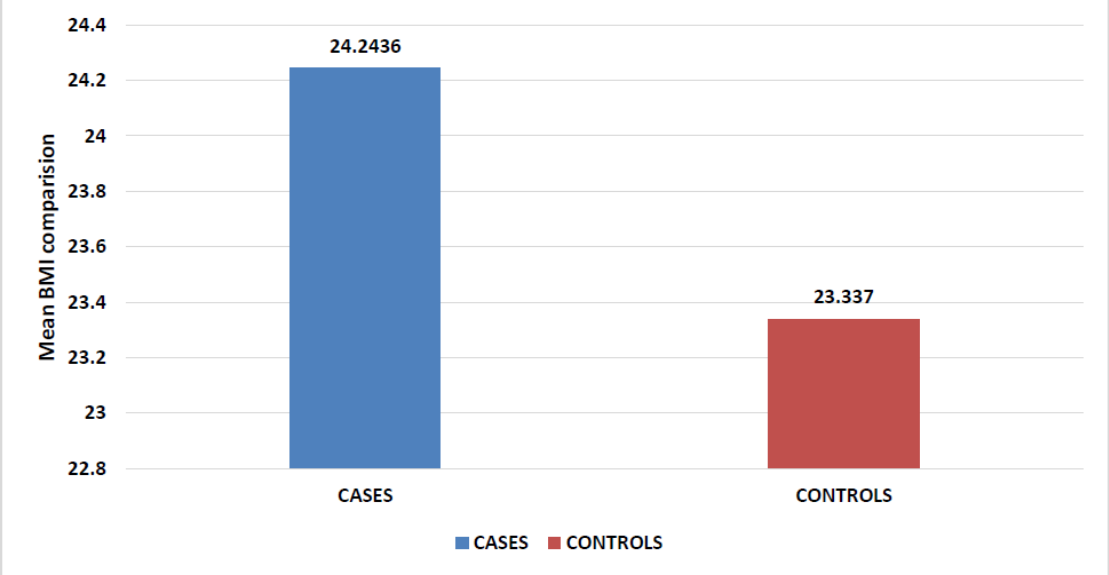

TABLE 4: RISK FACTORS ANALYSIS AMONG CASES

RISK FACTOR	SUB CATEGORY	FREQUENCY	PERCENTAGE
DIABETES	YES	14	28%
	NO	36	72%

TABLE 5: RISK FACTORS ANALYSIS AMONG CONTROLS

RISK FACTOR	SUB CATEGORY	FREQUENCY	PERCENTAGE
DIABETES	YES	13	26%
	NO	37	74%

Table 6: ODD'S RATIO

	CASES	CONTROLS	Total
Homocysteine >10	45(a)	12(b)	69
Homocysteine <10	5(c)	38(d)	31
Total	50	50	100

P value= 0.001

Exposure rate among cases = a/a+c= 45/45+5=45/50=0.9

Exposure rate among controls = b/b+d= 12/12+38=12/50=0.24

Odd's ratio= ad/bc= 45×38†5×12=28.5

5. DISCUSSION:

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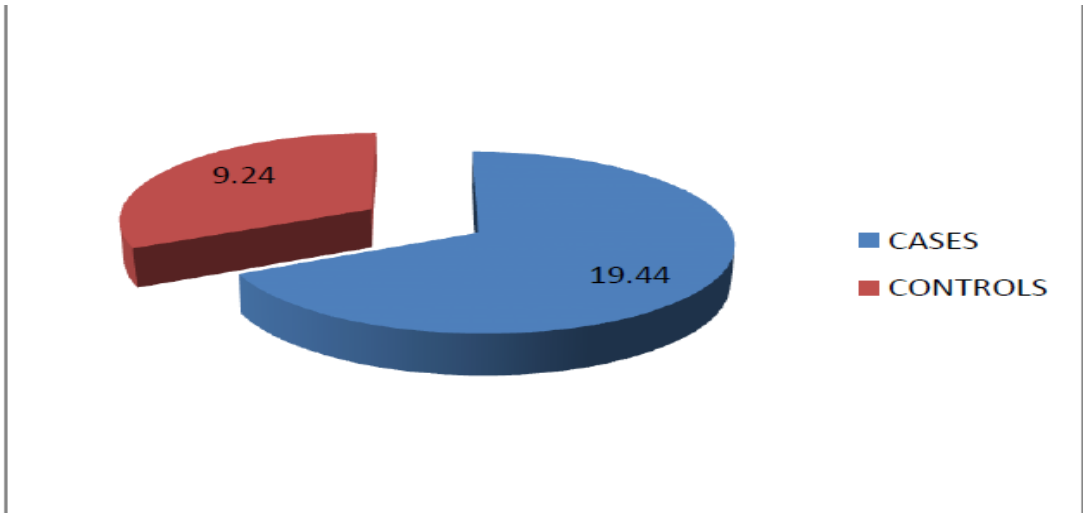
The present study comprised 50 patients of Ischaemic stroke and 50 asymptomatic controls. The mean Homocysteine values of all 50 patients were 19.44± 5.84, whereas, in controls, the mean values were 9.24 ± 1.93, the P-value is < 0.001. There is a statistical significance between the two values.

FIG-4 : MEAN HOMOCYSTEINE VALUES IN ISCHAEMIC STROKE PATIENTS AND CONTROLS



COMPARISON OF PATIENT GROUP AND CONTROL GROUP:

Inpatient group, the mean age is 60.68 and in that of the control group is 63.44, and the mean of the BMI in patients and control groups is 24.24 and 23.33, respectively.

So the present study included age, sex, and BMI matched individuals.

Homocysteine and DM:

In this present study, 14 patients had type 2 diabetes, and the rest of the 36 patients were non-Diabetics.

The mean homocysteine values in people with diabetes were 19.39 ± 5.76, and that in non-diabetics was 19.47± 5.97.

ODDS RATIO;

The ODDs ratio gives the strength of the association between a risk factor and stroke. In the present study out of 50 patients 45 had homocysteine levels >10 µmol/L whereas 5 had homocysteine levels < 10 µmol/L and out of the 50 controls 12 had homocysteine levels >10 µmol/L, and 38 had homocysteine levels < 10 µmol/L.

Calculation of relative risk:

1. Relative Risk:

Risk of stroke in those with risk factors

---------- = 6.14

Risk of stroke in those without risk factor

Exposure rate among cases = a/a+c= 45/45+5=45/50=0.9

Exposure rate among controls = b/b+d= 12/12+38=12/50=0.24

Odd‟s ratio= ad/bc= 45×38†5×12=28.5

2. ODD‟s ratio =

ODD‟s of stroke with risk factor

---------- = 28.5

ODD‟s of stroke without a risk factor

6. SUMMARY

The present study has shown an elevation of Homocysteine levels > 10 µmol/L in 89% of patients aged above 45 years. Dr. Nigel Tan et al. had found an elevation of homocysteine > 10 µmol/L in 78% of patients of Ischemic stroke aged above 45 years.

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The mean homocysteine levels among the 50 patients in the present study were 19.44 ± 5.84 in contrast to controls who had a mean value of 9.24 ± 1.93. There is a significant difference between the patients and the controls. The p-value is < 0.001 that is statistically significant.

A similar study was conducted by Dr. Nigel Tan, Dr. N. Venkata Subramanian et al. in which they had selected 109 cases and 88 controls. The mean Homocysteine values in cases were 15.7, and that of in controls was 9.8, with a p-value of < 0.001.

Hence plasma homocysteine levels are to be measured regularly among patients with Ischaemic stroke.

The British regional heart study, the Rotterdam study of the elderly, and the Framingham studies, which were cohort studies, have shown elevated plasma homocysteine levels in Ischaemic strokes.

TABLE -7: MEAN HOMOCYSTEINE LEVELS IN CASES AND CONTROLS

	Present study	Dr.Nigel Tan et al
Cases	19.44 ± 5.84	15.7
Controls	9.24 ± 1.93	9.8
p Value	< 0.001	< 0.001

RELATIVE RISK OF CEREBROVASCULAR DISEASE IS ASSOCIATED WITH AN INCREASE OF HOMOCYSTEINE LEVELS

Table - 8:

STUDY	RELATIVE RISK
Verhoel Study	2.8
Alfthan Study	3.6
Brattstrom Study	4.5
Araki, stroke Study	5
Coul, stroke Study	5.5
Present Study	6.14

7. CONCLUSION:

The present study was done to assess the role of homocysteine as an independent risk factor for ischemic stroke in patients greater than 45 years of age in risk factor of diabetes in cases and controls.

1. The mean Homocysteine values in patients above the age of 45 years were significantly elevated (19.44 ±5.84 Vs. 9.24± 1.93) than asymptomatic control (19.44 ±5.84 Vs. 9.24± 1.93). Hence Homocysteine should be assessed routinely in all patients with ischemic stroke.

2. The present study addresses the fact that diabetes is an important risk factors for ischemic stroke. The mean homocysteine levels were more in patients with risk factor group than in the non-risk factor group. This infers that patient with risk factors should be assessed for homocysteine levels and homocysteine is a predominant independent risk factor for ischaemic stroke.

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