A Retrospective Study of Homocysteine, Effects in Hypertensive Patients at Risk of Ischemic Stroke

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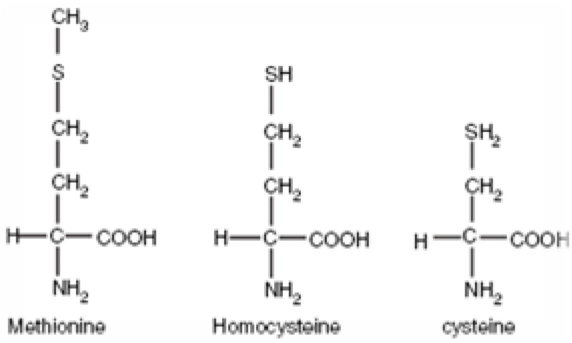
Abstract: ***A high level of homocysteine is a risk factor for Neurological Problems and Associated with heart disease. It's associated with low levels of vitamins B6, B12, and folate, as well as renal disease. Research has shown, however, that getting your homocysteine levels down with vitamins doesn't reduce your chance of having Neurological Problems and Associated with heart disease. A homocysteine test measures the amount of homocysteine in your blood. Homocysteine is a type of amino acid, a chemical your body uses to make proteins. Normally, vitamin B12, vitamin B6, and folic acid break down homocysteine and change it into other substances your body needs. There should be very little homocysteine left in the bloodstream. Hyperhomocysteinemia is associated with atherosclerosis, as it can be seen in inborn errors of methionine metabolism. Likewise, many studies have also reported more modest increases in serum homocysteine levels in other atherosclerotic disorders like cardiovascular disease and all types of stroke with a positive correlation with age. Homocysteine is a thiol containing amino acid known to be associated with various diseases and/or clinical condition including stroke, Alzheimer's disease, neural tube defects, schizophrenia, renal failure etc. An elevated level of homocysteine has also been implicated as an independent risk factor for cardiovascular diseases. In fact, in coronary artery disease (CAD) patients, homocysteine level is a significant predictor of mortality, independent of traditional risk factors. Association of a single amino acid with so many diseases warrants its capacity to alter some basic cellular processes or pathways. Therefore, it has become increasingly important to understand the mechanism involved in homocysteine induced disease pathogenesis. Further investigation of the relationship of homocysteine levels with age, diabetes mellitus, and hypertension, and the role of homocysteine as a risk factor for ischemic stroke should be carried out on a larger scale to prove its accuracy. The benefits of screening for homocysteine levels also need to be studied in the elderly, especially those with diabetes mellitus and hypertension, which can lead to timely prevention of strokes and ischemic heart disease with vitamin B supplements, and other appropriate interventions.***

Keywords: Pathway, Stroke, Paralysis, Hemiplegia

1. Introduction

General Overview

Homocysteine is a thiol containing amino acid. It was discovered in 1932 by two scientists, Butz and vigneaud. They heated methionine in sulfuric acid and a compound was isolated which had chemical properties similar to those of cysteine. The compound was found to be bis – (γ– amino – γ- carboxy propyl) disulfide and was named homocysteine since it was the next higher homologue of cysteine. They also proposed that homocysteine might support growth on cysteine deficient diet. After the discovery of homocysteine, Bernstein synthesized homocysteine thiolactone (a cyclic thioester) from methionine in 1934 which was characterized by the Vigneaud and coworkers. L-Homocysteine thiolactone is a stable form of homocysteine that can reconvert back to homocysteine by alkaline hydrolysis.

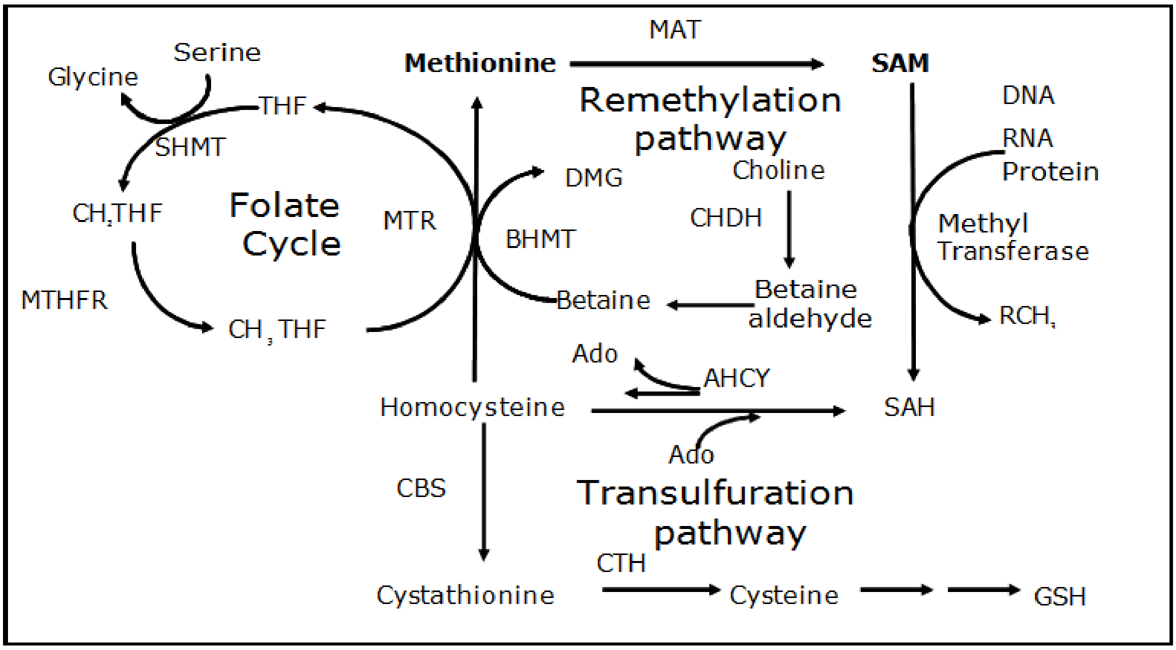


The structures of methionine, homocysteine and cysteine

Biologically homocysteine is formed during methionine metabolism inside the cell. The normal intracellular concentration of homocysteine is less than 1 µmol / L while 5-12 µmol/L homocysteine is normally present in the circulation (Ueland PM et. al., 1993). When the concentration of homocysteine becomes more than 12 µmol/L the condition is known as hyperhomocystenemia (elevated level of homocysteine).

Homocysteine Metabolism and Its Regulation

Homocysteine is a key branch point intermediate in the methionine cycle that is ubiquitously present in all the cells. Methionine from diet is converted to S-adenosyl methionine (SAM) by the enzyme S-adenosyl methionine synthase.



Methioine Cycle (Human)

Mechanism of Homocysteine Toxicity

Homocysteine is long known to be associated with various diseases but the exact mechanism of homocysteine induced pathogenesis is not yet clearly understood. Several hypotheses have been put forward to explain the deleterious effects of homocysteine. The possible mechanisms proposed for homocysteine induced pathogenesis include oxidative stress hypothesis, endoplasmic stress hypothesis, altered methylation hypothesis and molecular targeting hypothesis.

2. Background and Purpose

Total homocysteine level (tHcy) is a risk factor of ischemic stroke (IS) and coronary heart disease. However, the results are conflicting and mainly focused on healthy individuals in developed countries.

3. Methods

A Retrospective, population-based study was conducted among 55 participants from 15 communities in the city of Rajasthan (Kota & Udaipur). A Cox regression analysis was applied to evaluate the contribution of tHcy to the risk of IS and coronary heart disease. The effect of folic acid supplementation on tHcy levels was also evaluated among 55 patients with essential hypertension, who received an average of 1 years of folic acid supplementation.

4. Results

After adjustment for confounding factors, the hazard ratios (95% confidence intervals) of IS caused by hyperhomocysteinemia were 2.18 (1.65–2.89), 2.40 (1.56–3.67), and 2.73 (1.83–4.08) in the total, male, and female participants, respectively. Compared with normal levels of tHcy (<15 µmol/L), the hazard ratios (95% confidence intervals) for IS in the highest tHcy category (≥30 µmol/L) were 4.96 (3.03–8.12), 6.11 (3.44–10.85), and 1.84 (0.52–6.46) in the total, males, and females participants, respectively. However, we did not observe a significant relationship between tHcy and the risk of coronary heart disease. The 1 years of folic acid supplementation reduced tHcy levels by 6.7 µmol/L (27.92%) in patients with essential hypertension.

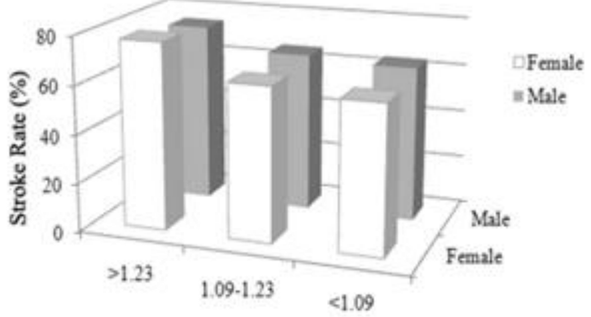
Variables	Males (n=35)	Females (n=20)	*P* Value	Total (n=5488)
Education, %				
<Middle school	203 (7.49%)	150 (5.40%)	0.0008	353 (6.43%)
Middle/high school	1846 (68.07%)	1863 (67.11%)		3709 (67.58%)
≥College	663 (24.45%)	763 (27.49%)		1426 (25.98%)
Smoking, %	745 (27.47%)	41 (1.48%)	<0.0001	786 (14.32%)
Alcohol consumption, %	1139 (42.00%)	307 (11.06%)	<0.0001	1446 (26.35%)
Salt intake, %				
Low (<6 g/d)	457 (16.85%)	531 (19.13%)	0.0066	988 (18.00%)
Moderate (6–13 g/d)	1959 (72.23%)	2000 (72.05%)		3959 (72.14%)
High (>13 g/d)	296 (10.91%)	245 (8.83%)		541 (9.86%)
Oil intake, %				
Low (<25 g/d)	361 (13.31%)	456 (16.43%)	<0.0001	817 (14.89%)
Moderate (25–40 g/d)	2029 (74.82%)	2081 (74.96%)		4110 (74.89%)
High (>40 g/d)	322 (11.87%)	239 (8.61%)		561 (10.22%)
Vegetables intake, %				
Low (<300 g/d)	210 (7.70%)	161 (5.75%)	0.0014	371 (6.72%)

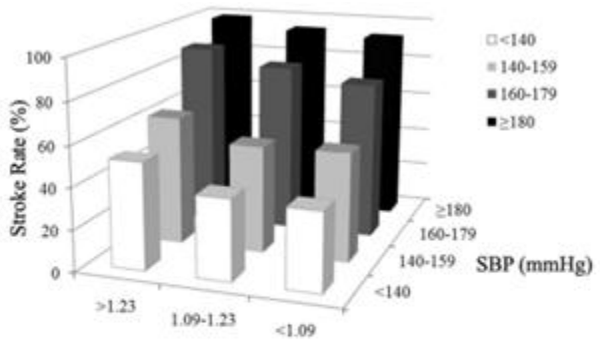
Moderate (300–500 g/d)	1845 (67.68%)	1862 (66.55%)		3707 (67.11%)
High (>500 g/d)	671 (24.61%)	775 (27.70%)		1446 (26.18%)
Fruit intake, ≥200 g/d, %	1934 (71.31%)	2237 (80.58%)	<0.0001	4171 (76.00%)
Physical activity, %				
<1 time/week	400 (14.75%)	349 (12.57%)	0.054	749 (13.65%)
1–3 times/week	1380 (50.88%)	1429 (51.48%)		2809 (51.18%)
>3 times/week	932 (34.37%)	998 (35.95%)		1930 (35.17%)
Depression, %	729 (26.88%)	779 (28.06%)	0.327	1508 (27.48%)
Years of hypertension, %				
<2	522 (19.25%)	602 (21.69%)	0.0026	1124 (20.48%)
2–5	834 (30.75%)	733 (26.40%)		1567 (28.55%)
5–10	640 (23.60%)	668 (24.06%)		1308 (23.83%)
≥10	716 (26.40%)	773 (27.85%)		1489 (27.13%)
Antihypertensive drugs	2179 (80.35%)	2176 (78.39%)	0.0728	4355 (79.35%)
Diabetic	277 (10.21%)	260 (9.37%)	0.2905	537 (9.78%)
High TC	170 (6.27%)	355 (12.79%)	<0.0001	525 (9.57%)
High TG	736 (27.14%)	638 (22.98%)	0.0004	1374 (25.04%)
High LDL	501 (18.47%)	639 (23.02%)	<0.0001	1140 (20.77%)
Age, y	57.07±13.04	59.68±11.01	<0.0001	58.39±12.13
BMI, kg/m^2	24.74±2.92	23.94±3.08	<0.0001	24.33±3.03
SBP, mm Hg	133.54±14.65	132.96±15.52	0.1525	133.25±15.1
DBP, mm Hg	84.9±10.52	82.49±10.23	<0.0001	83.68±10.44
TC, mmol/L	4.92±0.97	5.28±1.06	<0.0001	5.10±1.03
LDL, mmol/L	2.94±0.76	3.06±0.82	<0.0001	3.00±0.8
UA, μmol/L	378.11±92.21	308.47±84.62	<0.0001	342.89±95.06
TG, mmol/L*	0.52±0.58	0.46±0.52	<0.0001	0.49±0.56
Glucose, mmol/L	5.69±1.42	5.59±1.19	0.0058	5.64±1.31
Creatinine, μmol/L	89.11±17.38	67.76±13.49	<0.0001	78.31±18.85

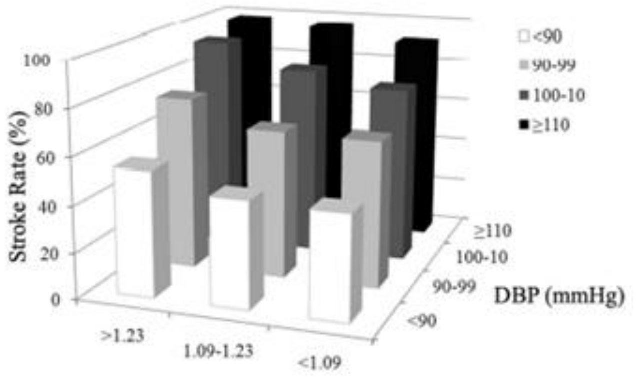
(The Baseline Characteristics of the Followed 55 Subjects According to Sex)
(Total sample size is 55, but for accuracy 5000 samples we have included)

tHcy, μmol/L			Hyperhomocysteinemia (≥15 μmol/L)		
n	means±SD	*P* Value	*n*,%	*P* Value	
Total	5935	13.60±1.52		1863 (31.39)	
Males	2928	15.96±1.55	<0.0001	1360 (46.45)	<0.0001
Females	3007	11.70±1.38		503 (16.73)	
Males					
<50 y	859	15.49±1.65	<0.0001	329 (38.30)	<0.0001
50–60 y	677	15.03±1.54		279 (41.21)	
60–70 y	772	15.64±1.48		367 (47.54)	
≥70 y	620	17.81±1.52		385 (62.10)	
Females					
<50 y	558	10.28±1.38	<0.0001	51 (9.14)	<0.0001
50–60 y	772	10.70±1.34		68 (8.81)	
60–70 y	1057	11.94±1.35		172 (16.27)	
≥70 y	620	13.74±1.40		212 (34.19)	
Total					
<50 y	1417	13.20±1.62	<0.0001	380 (26.82)	<0.0001
50–60 y	1449	12.55±1.49		347 (23.95)	
60–70 y	1829	13.46±1.43		539 (29.47)	
≥70 y	1240	15.64±1.49		597 (48.15)	

The tHcy Levels of Different Sex and Age







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