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COMPARATIVE STUDY OF HUMAN BETAINE HOMOCYSTEINE METHYLTRANSFERASE (BHMT) BETWEEN DISEASES

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ABSTRACT

For more than 20 years, moderately raised concentrations of total homocysteine (tHcy) have been associated with an increased risk of several diseases (atherothrombotic vascular, dementia, renal failure, autism and liver) events but only recently has evidence mounted to suggest that the association may be causal. The association is independent of other factors, it is fairly consistent across many studies, it is strong and dose-related, and it is biologically plausible. However, the evidence needs to be strengthened by a systematic review of all comparable studies and the demonstration, in randomized trials, that lowering tHcy is followed by a significant reduction in diseases. In addition, the measurement of tHcy needs to be standardized. If these can be achieved then tHcy measurement will become another useful marker of (disease) risk, multivitamin therapy will be another therapeutic option for people at risk of specific disease. And fortification of food with folic acid will rise high on the political and public health agenda. ***Objective:*** To assess homocysteine concentration in different diseases as a risk marker for patients.

KEYWORDS: (BHMT) Betaine Homocysteine Methyltransferase, (Hcy) Homocysteine, (CVD) Cardiovascular Disease. (AD) Alzheimer disease.

INTRODUCTION

Homocysteine is a non-protein, naturally occurring amino acid of potential clinical significance. It is a homologue of the amino acid cysteine. Homocysteine was obtained in 1935 by the reduction of homocysteine with metallic sodium in ammonia.[1]

The relationship between different factors (genetic, physiological, lifestyle, as well as a variety of pathological conditions) and the level of homocysteine in plasma and urine was the subject of numerous studies. Homocystinuria, an inherited disease being the result of homozygous Cystathionine -β-synthase (CBS) deficiency and characterized by episodes of thromboembolism, As well as mental retardation, hepatic steatosis, lens dislocation, and osteoporosis was recognized as a risk factor for human diseases and described in 1960s by Carson and Niell, who found large quantities of homocysteine in the urine of siblings with mental retardation.[2,3]

At the same time, during biochemical investigations of children with homocystinuria was described by Gerritsen[4][5] demonstrated that homocystinuria is caused by the deficiency or absence of cystathionine synthase. In 1969, McCully noted a link between the elevated levels of homocysteine in blood and atherosclerosis. Since the early 1990s homocysteine has become the subject of a growing number of worldwide studies and the leading theme of many international conferences.

The mainstream of research examines the impact of elevated levels of homocysteine in cardiovascular[6] and neural tube defects[7,8] mental illness, and cognitive impairment.[9] Homocysteine is a sensitive indicator of subclinical folate or vitamin B12 deficiencies, rather than a standard hematologic indicator. For example, in uremic patients without other evidence of folate deficiency, folate supplementation reduced the degree of hyperhomocysteinemia, but did not consistently restore the level of homocysteine to its normal value.[10]

The connection between autism spectrum disorders (ASD) and hyperhomocysteinemia was presented for the first time by Paşca.[11]

Homocysteine is an amino acid, which plays several important roles in human physiology. A wide range of disorders, including neuropsychiatric disorders and autism, are associated with increased homocysteine levels in biological fluids. Various B vitamins: B6 (pyridoxine), B12 (cobalamin) and B9 (folic acid) are required as co-factors by the enzymes involved in homocysteine metabolism. Therefore, monitoring of homocysteine levels in body fluids of autistic children can provide information on genetic and physiological diseases, improper lifestyle (including dietary habits), as well as a variety of pathological conditions.

SUBJECT, MATERIAL AND METHOD

Seventy five patients with different diseases were enrolled in this study, their age range from 10 to 81 years. They were seeking treatment for their diseases in (Ibn-Roshed, Ibn-Alnafees, Alkindy Hospitals and private clinics) in Baghdad from January 2015 to June 2015.

The diagnosis of each case was established by clinical examination done by a specialized Analysis systems such as (Homocysteine, Urea, Creatinine, glucose and Thyroid function tests).

The patients were subjected to questionnaire about name, age, gender, disease duration, type of drug, drugs duration. They were divided into eight groups: each group consisted of ten recently diagnosed in the diseases.

Forty healthy volunteers whose ages and gender were considered as control group. All of them received no treatment with no complaint of other chronic or systemic diseases; their age range was (10 to 38) years Blood samples were collected from all patients and controls to assess serum concentrations of homocysteine by enzyme-linked immune-sorbent assay.

The ethical committee of College of science /Al-NahrainUniversity approved this study and all samples were obtained with informed consent in accordance with the Baghdad teaching hospital declaration.

Statistical Analysis

Analysis of data was carried out using the available statistical package of SPSS-22 (Statistical Packages for Social Sciences- version 22).

Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values).

The significance of difference of independent means (quantitative data) were tested using Students-t-test for two independent means. Statistical significance was considered whenever the P value for the test of significance was equal or less than 0.05.

RESULT AND DISCUSSION

The results showed that (Hcy) level varies depending on the type of disease, table (1). An interesting significant increase of mean serum homocysteine level was recorded in Liver

disease. An interesting homocysteine level in Liver disease between all studied groups, while the lowest mean Hcy concentration was in Hyperthyroidism individuals compared to healthy adults and children (Control) individuals with P-value <0.005.

Table (1) List of homocysteine level in diseases and normal individuals

Sample type	Homocysteine concentration (pg/ml)	
	Mean±SD	(Range)
Liver disease	171.50±93.92	(88.00-410.00)
Alzahymer disease	107.07±15.81	(80.80-135.10)
Diabetes	77.00±55.01	(28.40-160.00)
Heart disease	86.73±22.79	(54.30-120.40)
Hypothyroidism	45.62±13.85	(27.80-67.90)
Hyperthyroidism	29.36±6.71	(19.30-40.90)
Renal failure	152.30±38.84	(100.00-219.00)
Normal adults	10.31±2.63	(6.80-14.70)
Children with autism	66.80±25.45	(31.90-91.50)

Detection of homocystiene in liver disease

Serum homocystiene concentration levels in the first group were found to increase significantly in liver 171.50±93.92 compared to healthy control 10.31±2.63 with p< 0.001. The study recorded the highest concentration number of homocystiene among all diseases it can be seen in table and figure (2).

The results showed that the total Hcy concentrations were significantly higher this patients group irrespective of age or gender than in the control group. Other studies showed that the highest total Hcy concentrations were in patients aged (60-69) years, (both sexes).[12]

Who concluded that aging gradually increases Hcy blood concentration. It was also shown that Hcy concentration in men was not significantly different from that of women(10), this is similar to our findings. The elevated Hcy concentrations seen in patients with liver cirrhosis might be explained in part by tissue damage occurring directly through increasing Hcy leakage or indirectly by initiated cell repair.[13]

Table (2) List of homocysteine Conc. in liver disease and normal individuals.

Sample	Homocysteine concentration pg/mL			
	n	Mean ± SD	Range	p-value
Control	40	10.31±2.63	4.713- 6.033	< 0.001
Liver	10	171.50±93.92	88.00-410.00	

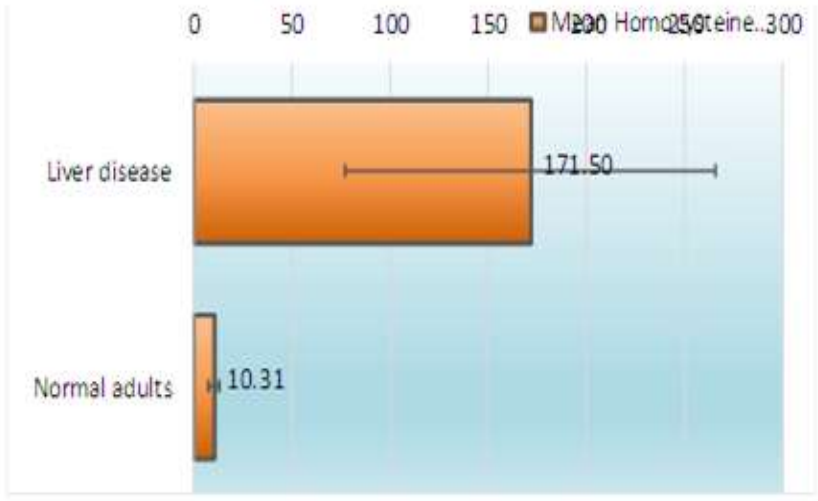

Figure (2) Homocysteine Conc. in liver disease and normal individuals

Detection of homocystiene in Cardio Vascular Disease (CVD)

Table and figure (3) present data indicated that there was high concentration of homocystiene in cardiovascular disease patients group 86.73±22.79 pg/ml. with highly statistical significant difference ($p<0.001$) when compared with healthy control group and the mean results of male and female was 95.15±25.60, 74.10±10.55 pg/ml. with P-value ($P<0.163$).[14] demonstrated increasing of serum homocysteine in diabetic, metabolic syndrome and atherosclerosis and concluded that homocysteinemia being an independent risk factor for cardiovascular disease as occurs in thrombotic events (such as arterial and venous occlusion) and ischemic disease such as stroke and myocardial infarction (two of the most common causes of death and disability).

With an aging population who are at greater risk of developing these morbid and mortal cardiovascular diseases associated with metabolic syndrome, diabetic and atherosclerosis, there should exist a dedicated consideration for folate and possible cobalamin supplementation, in addition to global risk reduction among them.

Table (3) List of homocysteine level in diseases and normal individuals

Sample	Homocysteine concentration pg/mL			
	n	Mean ± SD	Range	p-value
Control	40	10.31±2.63	4.713- 6.033	< 0.001
Heart disease	10	86.73±22.79	88.00-410.00	

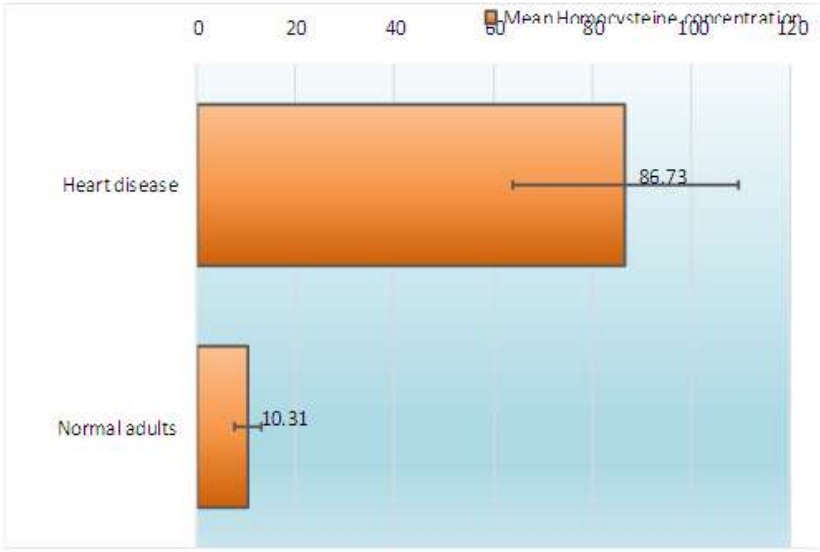

Figure (3) List of homocysteine level between control and CVD

Detection of homocystiene in Alzheimer disease (AD)

Serum homocystiene concentration levels in this group demonstrated significant difference with p< 0.001 when compared to healthy control subjects 171.50±93.92, 10.31±2.63 respectively. The study showed positive relationship with age range as in table and figure (4) below. The results of our prospective, observational study indicate that there is a strong, graded association between plasma total homocysteine levels and the risk of dementia and Alzheimer's disease. An increment in the plasma homocysteine level of 5 µmol per liter increased the risk of Alzheimer's disease by 40 percent. A plasma homocysteine level in the highest age-specific quartile doubled the risk of dementia or Alzheimer's diseas.[15]

Table (4) List of homocysteine level in Alzheimer disease and normal individuals

Sample	Homocysteine concentration pg/mL			
	n	Mean ± SD	Range	p-value
Control	40	10.31±2.63	4.713- 6.033	< 0.001
Alzheimer	10	171.50±93.92	88.00-410.00	

Detection of homocysteine in Renal failure

The second highest homocystiene concentration levels was recorded in Renal failure 152.30±38.84 for this study the concentration was increased significantly with p< 0.001. these finding illustrated in table and figure (5) as compared to control individuals group 10.31±2.63. This disease associated with serum urea and createnine the more high urea Conc. was recorded high (positive relationship). As indicated in the present study, there is a significant elevation in the mean level of homocysteine in hemodialysis patients compared to

controls. This means that high homocysteine levels are linked to ESRD. Such finding is in agreement with that demonstrated by.[16][17]

Table (5) List of homocysteine level in Renal failure and normal individuals

Sample	Homocysteine concentration pg/mL			
	n	Mean ± SD	Range	P value
Control	40	10.31±2.63	9.70-10.03	< 0.001
Renal failure	10	152.30±38.84	100.00-219.00	

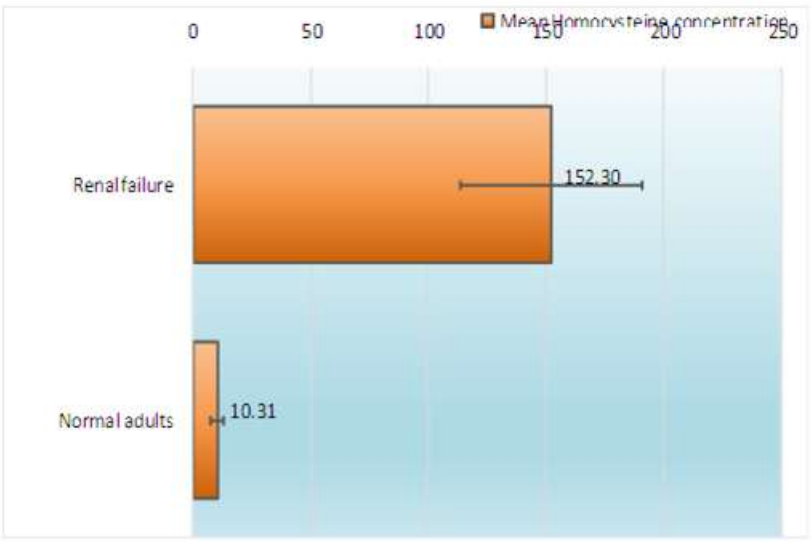

Figure (5) Homocysteine level in Renal failure and normal individuals

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