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Original Research Article

Evaluation of serum folate, vitamin B12 and homocysteine among blood donors in Lagos State University teaching hospital, Lagos, Nigeria

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ABSTRACT

Background: Folate, vitamin B12 deficiency and hyperhomocysteinaemia have been reported as important risk factors for the development of cardiovascular events and ischaemic stroke. These vitamin deficiencies are also implicated in the pathogenesis of several diseases like anaemia, dementia, Alzheimer's disease and cancers. This study determined the serum levels of vitamins B12, folate, and homocysteine among blood donors in the Lagos State University Teaching Hospital, Ikeja, Lagos, Nigeria.
Methods: This was a descriptive, cross-sectional study done among blood donors at the donor clinic of LASUTH Ikeja, Lagos, Nigeria. One hundred blood donors who met the donor inclusion criteria of LASUTH were recruited consecutively into the study. Five ml of venous blood was collected from each consenting participant into ethylene Diamine Tetra-acetic Acid (EDTA) and plain bottles for the determination of full blood count and folate, vitamin B12/homocysteine respectively. Data were analyzed with statistical package for social science version 23.0, the p value was set at ≤0.05.
Results: The mean age of the study participants was 33.36±8.31 years. The mean serum homocysteine, folate and VitB12 levels among the study participants were 5.59±9.14 nmol/l, 21.57±4.15ng/ml and 1694.38±592.83 pg/ml respectively. About 8% of the study participants had serum homocysteine levels more than 15nmol/L, 4% had vitamin B12 levels less than 203pg/ml while all 100 participants had normal folate levels of 4ng/ml and above.
Conclusions: The prevalence of hyperhomocysteinemia, vitaminB12 and folate deficiencies among blood donors in LASUTH is low.

Keywords: Blood donors, Folate, Vitamin B12, Homocysteine, ELISA

INTRODUCTION

Hyperhomocysteinaemia (concentrations above15µmol/l) has been recognized as a particular risk factor for stroke and atherosclerosis in young adults and studies have established the fact that total plasma homocysteiene (tHcy) is an independent, graded and strong risk factor for the development of stroke and coronary heart disease.[1,2] In addition, some studies have demonstrated that elevated homocysteiene levels are associated with higher mortality rates from coronary heart disease and stroke. [3] Homocysteine (Hcy) is a toxic, sulfur-containing

intermediate of methionine metabolism.[4] Hyper-homocysteinemia (hHcy), as a consequence of impaired Hcy metabolism or defects in crucial co-factors that take part in its recycling, is assumed as an independent human stroke risk factor.[4] Nutritional and genetic factors have been implicated in disturbance of homocysteine metabolism.[5] Low plasma concentrations of one or more B vitamins contribute to approximately two-third of all cases of hyperhomocysteinaemia.[6] Epidemiologic studies have established an association between elevated homocysteiene and increased risk of cardiovascular diseases (atherosclerosis, coronary artery disease, ischaemic stroke among others).[7]

Serum levels of homocysteiene is increased by some disorders like pernicious anaemia, chronic renal failure, acute lymphoblastic leukaemia, cancer in the breast, pancreas and ovary, hypothyroidism, smoking and drugs such as theophylline, phenytoin and methotrexate.[8] Elevated levels of plasma homocysteine can result from many factors, like genetic defects of homocysteine metabolism, vitamin deficiencies and renal impairment. The deficiency of one or more B vitamins contributes to approximately two-thirds of all cases of hyperhomocysteinemia.[5] Vitamin supplementation can normalize high homocysteine concentrations; however, it is uncertain if normalizing homocysteine concentrations improves cardiovascular morbidity and mortality. Hyperhomocysteinemia is related to an increased risk for atherosclerosis development, which can lead to coronary artery disease, myocardial infarction and stroke.[8-12] Other pathological consequences include peripheral vascular diseases (deep vein thrombosis, pulmonary embolism and intermittent claudication), dementia, Alzheimer's disease (AD) and obstetric complications (preeclampsia, placental abruption and pregnancy loss).[11-14]

Folic acid (vitamin B9) is a requirement for erythropoiesis and also plays a vital role in normal brain functioning, mental health and emotional health. Sources of Folic acid include dark leafy vegetables, liver, beef, kidney etc. Folic acid is needed for DNA methylation, repair, and synthesis.[15] Its deficiency is associated with megaloblastic anaemia, neuropsychiatry defect, and cancers because of its involvement in histidine, serine, glycine, methionine, purine, and thymidylate cycles.[16] Vitamin B12 also known as cobalamin is the largest of the B group of vitamins and exists in nature as methylcobalamin and adenosyl-cobalamin. Dietary sources of vitamin B12 include beef, liver, eggs, and dairies.[17] Vitamin B12 is used in two forms by the body namely, methylcobalamin needed as a cofactor for methionine synthetase in the conversion of homocysteine to methionine, the latter is used for DNA methylation, secondly, 5-deoxyadenosyl cobalamin which converts methylmalonyl CoA to succinyl CoA, the latter is used in the production of haemoglobin.[18] Deficiencies of both folate and vitamin B12 result in increased total homocysteine because both substances are involved in the conversion of homocysteine to methionine, elevated methylmalonic acid (MMA) is particularly specific to vitamin B12 deficiency. MMA can therefore be used as a biomarker of vitamin B12 deficiency.[19-21] The aim of this study was to determine the prevalence of hyperhomocyteinaemia, folate and vitamin B12 deficiencies among blood donors.

METHODS

Study location, population and design

The study was done at the donor clinic of the Lagos state University Teaching Hospital (LASUTH). LASUTH was established as a cottage hospital in 1955 and transformed into a secondary health center in 1970, and later metamorphosed into a teaching hospital in July 2001 following the establishment of Lagos state university college of medicine on 9 February 1999. The participants of the study were recruited from the donor clinic of LASUTH which operates six days a week from Monday to Saturday. Current study was a descriptive, cross-sectional study.

Inclusion criteria

All donors who gave informed consent and met the donor inclusion criteria of LASUTH were recruited into the study. Donor inclusion criteria include; age: 18-60 years, weight and height: minimum of 50 kg and 5 feet respectively, haemoglobin level: not less than 12.5g/dl, at least 12 weeks interval between donations, blood pressure: Not greater than 140/90 mmHg, pulse rate: 50-100 beats/min and temperature: 36.6^{o}C-37.2^{o}C.

Exclusion criteria

All donors who refused to give informed consent and those who failed to meet the inclusion criteria as outlined above were excluded from the study.

Sampling technique

Participants were recruited consecutively as they consented to participate in the study till the desired sample size was reached.

Questionnaire administration and history taking

With the use of an interviewer-administered questionnaire, each participant was interviewed to obtain relevant socio-demographic and clinical data like age at last birthday, history of blood transfusion, and drug history, particularly use of folic acid tablet and other haematinics.

Specimen collection

Following receipt of written consents from the participants, from intravenous access, under aseptic conditions using a vacutainer needle and bottle, 5 ml of

blood was collected into an EDTA bottle to obtain a blood sample for Haemoglobin, Packed cell volume, Red cell count, red cell indices, total white blood cell count with differentials, and platelet counts. Another 3 ml was collected into plain bottle and content centrifuged to obtain the serum for the folate, vitamin B12 and homocysteine using enzyme-linked immunosorbent assay (ELISA). Sera from plain bottles were stored at -40˚C for ELISA of folate, vitamin B12 and, homocysteine. All assays were done in the haematology laboratory in LASUTH. The full blood count was carried out using automated haematology analyser KX-21 manufactured in Germany. A commercial ELISA kit manufactured by axis-shield diagnostics, United Kingdom was used for the quantitative determination of holotranscobalamin (HoloTC)/active-B12 in serum. A commercial ELISA kit manufactured by USCN life science incorporation; USA was used for the quantitative determination of folate in serum. A commercial ELISA kit manufactured by axis-shield diagnostics; United Kingdom was used for the quantitative determination of serum homocysteine. Participants were not identified by their names and electronic data were pass-worded in the storage facility.

Statistical analysis

Data were analyzed using SPSS version 23.0 (statistical Package for Social Sciences, Inc., Chicago, Ill). The continuous variables were given as means±standard deviation (SD). The Pearson Chi-squared test was used to test for association between discrete variables, p value was considered to be statistically significant when ≤0.05.

RESULTS

Socio-demographic characteristics of study participants

A total of hundred (100) participants were recruited consisting of 5 (5%) females and 95 (95%) males. The mean age of the participants was 33.36±8.31 years with a minimum age of 19 years and maximum age of 55 years. A total of 67%, 29%, 3%, and 1% had tertiary, secondary, primary and no formal education respectively.

Haematological parameters of study participants

Haematological parameters of study participants are presented in (Table 1).

Table 1: Haematological parameters of all participants.

Parameters	Observations
PCV (%)	39.96±6.07
MCH (pg)	29.31±6.05
MCV (fl)	82.98±6.45
MCHC (g/dl)	34.35±1.49
WBC count x 10^9/l	6.17±1.91
Platelet count x 10^9/l	147.94±71.34

Serum homocysteine, folic acid and vitamin B12 levels among the participants

Serum homocysteine, folic acid and vitamin B12 levels among the study participants are presented in (Table 2, Figures 1-3).

Table 2: Serum homocysteine, folate and vitamin B12 of study participants.

Variable	Min	Max	Mean±SD
Homocysteine (nmol/l)	0.60	45.00	5.59±9.14
Folate (ng/ml)	15.00	29.00	21.57±4.15
Vitamin B12 (Pg/ml)	40.00	3020.00	1694.38±592.83

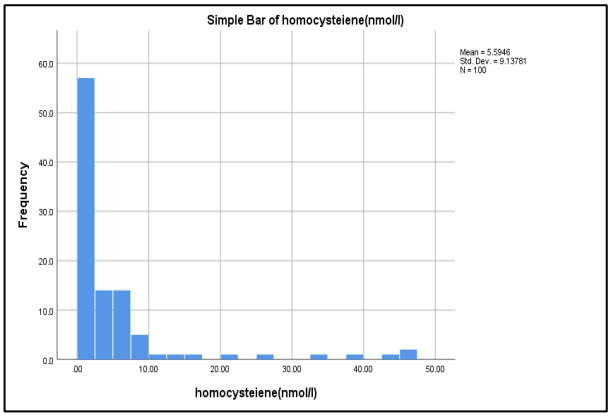

Figure 1: Serum homocysteine levels among study participants.

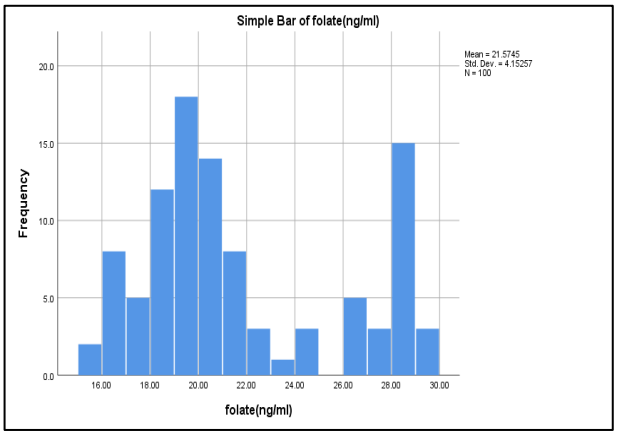

Figure 2: Serum folate levels among study participants.

Prevalence of hyperhomocysteinaemia, vitamin B12 and folate deficiency among study participants

Whilst none of the 100 participants had serum folate levels less than 4 ng/ml, 4% had vitamin B12 levels less that 203 pg/ml and 8% had elevated homocysteine levels (≥15 nmol/l) (Table 3).

Correlating the mean MCV with mean serum vitamin B12 and folate levels among the study participants

There was a significant positive correlation between the mean MCV and the means of the vitamin B12 and folate levels with p=0.001 in both cases (Table 4).

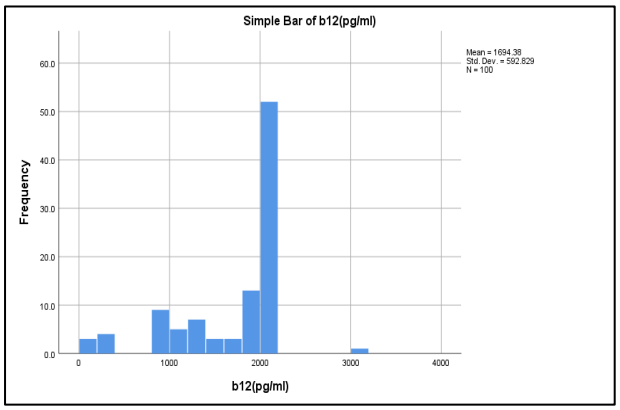

Figure 3: Serum vitamin B12 levels among study participants.

Table 3: Prevalence of hyperhomocysteinemia, vitamin B12 and folate deficiency.

Parameters	Prevalence (%)
Homocysteine (nmol/l)	8
Folate (ng/ml)	0
Vitamin B12 (pg/ml)	4

Table 4: Correlating mean MCV levels with mean vitamin B12 and folate levels.

MCV vs. parameters	P value
Vitamin B12 (pg/ml)	0.001
Folate (ng/ml)	0.001

DISCUSSION

Vitamin cofactors (folate and vitamin B12) are required for homocysteine metabolism and their deficiencies may promote hyperhomocysteinaemia. Furthermore, homocysteine's re-methylation to methionine via the acquisition of a methyl group from the conversion of 5-methyltetrahydrofolate to tetrahydrofolate links the folate cycle with homocysteine metabolism.[22,23] This pathway needs vitamin B12, the enzyme methionine synthase (MS) which is found in all organs of the body, and enzyme 5, 10-methylenetetrahydrofolate reductase (MTHFR) and folic acid that enters the cycle as tetrahydrofolate (THF). Thus, it is important to assay folic acid and vitamin B12 along with homocysteine. The mean homocysteine level was 5.59±9.14 nmol/l. Even though this is within normal (<15 nmol/l), it is higher than the level documented by Akande et al who assayed homocysteine levels in 58 healthy volunteers in Northern Nigeria, but lower than that obtained in a population of young healthy Italian blood donors.[24,25]

Homocysteiene levels obtained may be methodology-dependent. The wide difference in the homocysteiene levels from various studies could be accounted for by the different methods of homocysteiene assay used. The present study used enzyme linked immunosorbent assay for the evaluation of serum homocysteiene unlike that by Okubadejo et al where fluorescence polarization immunoassay method was used which does not require separation or washing steps.[26] Several studies done in different countries have been done to document normal serum levels of homocysteine. Unfortunately, results obtained are usually difficult to compare due to differences in cut-off values used, lifestyle, dietary habits, etc.[25]

Our study documented a mean serum homocysteine level of 5.59±9.14nmol/l with a range of 0.60-45.00 nmol/l; the prevalence of hyperhomocysteinaemia (levels ≥15 nmol/l) was 8%. Elevated homocysteiene levels in the blood (hyperhomocysteinaemia) increases the likelihood of endothelial cell injury which can lead to inflammation in the blood vessels.[27] A resultant ischaemic injury is observed following atherogenesis from the inflamed blood vessels. Hyperhomocysteinaemia has been further classified into moderate if plasma t-Hcy concentrations is 15-30 µmol/l, intermediate when plasma t-Hcy concentrations are 31-100 µmol/l, while severe when plasma t-Hcy levels are above 100 µmol/l).[27] Thus, hyperhomocysteinaemia is therefore a likely risk factor for coronary artery disease with resultant blockage of blood flow to the coronary arteries by an atherosclerotic plaque. Hyperhomocyteinaemia has also been found to be associated with early pregnancy losses and also with neural tube defects.[29] Homocysteine induces vascular injury via several mechanisms. Oxidative stress due to the formation of oxygen free radicals produced due to the oxidation of reduced homocysteine can cause direct injury to endothelial cells.[30] In addition, homocysteine has prothrombotic properties such as reduction of endothelial cell tissue plasminogen activator binding sites, activation of factor VIIa and V, inhibition of Protein C, increased fibrinopeptide, impaired thrombomodulin function and increased blood viscosity and these have been demonstrated in acute coronary syndromes.[31-33] None of our study participants had folate deficiency with all 100 of them having levels >4 ng/ml; the range in our study was 15-29 ng/ml with a mean of 21.57±4.15 ng/ml. Folate levels in the body can be measured both in serum and red blood cells of individuals. We measured levels in serum alone. Red blood cell folate is a better index of body folate stores as serum folate is affected by recent ingestion of folate; a reduced concentration of serum folate is used as an early marker of folate deficiency.[34-36]

Folate deficiency is dangerous especially in women where it has been associated with neural tube defects. It is now well established that the routine use of peri-conceptional folic acid supplementation has greatly reduced the first occurrence and recurrence of neural tube

defects in addition to other adverse birth outcomes.[37-38] Vitamin B12 deficiency is usually associated with neuropsychiatric symptoms which usually precede the haematological manifestations. Four (4%) of participants in our study had vitamin B12 levels less than the normal value of 203pg/ml. This is in sharp contrast to the study done by Renata and colleagues also among blood donors where they found that only 25% of their study population had adequate vitamin B12 levels.[39] Vitamin cofactors (folate, vitamin B_{12}, and vitamin B_6) are required for homocysteine metabolism and their deficiencies may promote hyperhomocysteinaemia. Furthermore, homocysteine's re-methylation to methionine via the acquisition of a methyl group from the conversion of 5-methyltetrahydrofolate to tetrahydrofolate links the folate cycle with homocysteine metabolism.[22,23] This pathway needs vitamin B12, the enzyme methionine synthase (MS) which is found in all organs of the body, and enzyme 5, 10-methylenetetrahydrofolate reductase (MTHFR) and folic acid that enters the cycle as tetrahydrofolate (THF). Interestingly, none of the participants in our study with elevated serum homocysteine had either folate or vitamin B12 deficiencies. Our study found a positive correlation between mean MCV and mean vitamin B12 and folate levels. Vitamin B12 and folate deficiencies are common causes of macrocytosis. This is because DNA synthesis requires cyanocobalamin (vitamin B12) and folate as cofactors and so a deficiency of the vitamin leads to decreased DNA synthesis in the erythrocyte, thus resulting in macrocytosis. Despite this relationship, the sensitivity of MCV for vitamin B12 deficiency was seen to be low (17%) in a study by Oosterhuis and colleagues and so dependence on MCV levels alone as a trigger for investigating patients for Vitamin B12 deficiencies may lead to undue diagnostic delays.[40]

Limitations

Limitations of the current study were since the study was self-funded by the authors and so the sample size was small; it may therefore be difficult to generalize conclusions. In addition, due to financial constraints, authors were unable to correct for renal impairment in the assessment of serum homocysteine.

CONCLUSION

VitaminB12 and folate deficiencies are uncommon in the blood donor population in LASUTH and the prevalence of hyperhomocysteinemia was also seen to be low among them. It may therefore not be a common cause of anaemia in our environment and in the evaluation of patients with anaemia, it may not be cost effective to assay these analytes.

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