Original Research Article

**SELENIUM AND GLUTATHIONE PEROXIDASE LEVELS IN PERSONS WITH EPILEPSY AND HEALTHY CONTROLS IN TWO TERTIARY HOSPITALS IN NORTH WEST NIGERIA: A COMPARATIVE STUDY**

**ABSTRACT:**

**Introduction**: Oxidative stress and increased reactive oxygen species have been implicated in recurrent seizures, but selenium containing glutathione per-oxidase are reported to protect against oxidative damage and promote neuronal cell survival.

**Aim:** We compared levels of selenium and glutathione peroxidase in persons with epilepsy (PWE) and healthy controls.

**Study Design**: A hospital-based cross-sectional case-control study.

**Place and Duration of Study:** This study was carried out from June to December 2014 at neurology outpatient clinics of Ahmadu Bello University Teaching Hospital (ABUTH) Zaria and Neuropsychiatry Hospital Barnawa, Kaduna.

**Methodology:** We collected blood samples from three categories each of 35 subjects (AED-naïve; AEDs-experienced, and healthy controls) after ethical approval and informed consent, for determination of serum selenium and glutathione peroxidase using Atomic Absorption Spectroscopy and ELISA methods respectively. Statistical analysis was done using ANOVA followed by Bonferroni post hoc test, and significant level was defined as *P* ≤ 0.05.

**Result:** The mean age ± SEM of the controls, patients on AEDs and new patients were 33.31 ± 1.80, 33.91 ± 2.35 and 31.25 ± 2.48 years respectively with no significant difference (*P* = 0.091). In each study group majority of them, 22 (62.9%) were male and 13 (37.1%) were female. Selenium level was significantly higher in AED-experienced PWE than AED-naïve PWE (*P* = 0.001) and healthy controls (*P* = 0.000), but was not significantly different between AED-naïve PWE and healthy controls (*P* = 1.000). Glutathione peroxidase level was significantly lower in AED-experienced PWE than AED-naïve PWE (*P* = 0.000) and healthy controls (*P* = 0.000), and also significantly lower in AED-naïve PWE than healthy controls (*P* = 0.01). Selenium correlated negatively with GPX (r = - 0.289, *P* = 0.003). There was no significant relationship between selenium, GPX with clinical variables like age at onset, duration of illness, seizure frequency and seizure type (*P* > 0.05).

**Conclusion:** Selenium level in the follow up group (ASM – experienced) was significantly higher than the new patients (ASM- naïve) and healthy controls. GPX level in ASM – experienced PWE was significantly lower than ASM - naive and healthy controls.

***Key words:*** *Epilepsy,**Selenium****,*** *Glutathione peroxidase, Persons with epilepsy, Seizure*

1. **INTRODUCTION:**

Epilepsy is one of the most common serious disorders of the brain, affecting about 70 million people worldwide and accounts for 0.5% of the global burden of diseases.1,2 World Health Organization globally estimated that 5 million people are diagnosed with epilepsy yearly and about 60% of patients with the illness receive no treatment.3,4 It is a major public health problem with serious social, cultural, psychological, and economic implications.5 Majority of people with epilepsy are found in developing countries in sub-Saharan Africa. About 25 million people have been reported to have the disease in Africa. Incidentally, despite the huge burden of epilepsy in Africa, adequate patient care and support are grossly lacking.4

A systematic review and meta-analysis by Owolabi et al put the prevalence rate in Nigeria at 8 per 1000 population.6 Epileptic seizures could be characterized by focal or generalized convulsions, loss of consciousness or periods of altered awareness associated with special sensory, somatosensory, psychic, autonomic symptoms and/or automatism.6 Although anti-seizure medications (ASMs) are the mainstay of epilepsy treatment, their use is merely to reduce frequency of the seizure as they do not produce curative effects and indeed the disease may be refractory to many of the available ASMs.3

Persons with epilepsy (PWE) have recurrent unpredictable seizures occurring spontaneously causing increased production and accumulation of reactive oxygen species (ROS) and a subsequent decline in the brain's antioxidant defenses. This results in increased oxidative stress and subsequent neuronal death and brain damage. 7,8 To mitigate the cellular damages caused by ROS; mammalian cells including humans have developed an antioxidant defense mechanism to neutralize the deleterious effects of ROS.9 These are enzymatic and non-enzymatic antioxidant mechanisms aimed at counteracting the effects of ROS.10 Therefore, worsening of epileptic seizures can occur when there is excessive production of ROS and decreased antioxidant activity. 11 Hence anything that enhances the antioxidant activity of the brain during epileptic seizure is thought to have a neuroprotective effect. 12

Selenium (Se) is an essential trace element necessary for several metabolic functions and protects the body from ROS. It is postulated to play a role in preventing epilepsy because of its antioxidant effects and ability to reduce oxidative tissue damage.13 Selenium exerts its protective benefit mainly through selenium-dependent antioxidant enzymes and seleno-proteins such as glutathione peroxidase (GPX). 14 Studies have shown that selenium deficiency can cause degeneration of GABAergic neurons which can lead to impaired neuronal function as can be seen in epilepsy and some other neurodegenerative diseases. 15 Reports concerning selenium and GPX levels in patients with epilepsy are conflicting. This study compared the levels of selenium and GPX among healthy controls; ASM-experienced PWE; ASM-naïve PWE and explored their relationship to the clinical characteristics of PWE.

1. **MATERIALS AND METHODS**

**2.1 Study Design:** This was carried out as a hospital-based cross-sectional case-control study.

**2.2 Ethical Consideration:** Ethical approval of study was granted by the Health Research Ethics Committee (HREC) of both Institutions before study commencement. All participants gave their informed written consent with strict confidentiality maintained in the course of the study.

**2.3 Study Site and participants**: This study was carried out from June to December 2014 at neurology outpatient clinics of Ahmadu Bello University Teaching Hospital (ABUTH) Zaria and Neuropsychiatry Hospital Barnawa, Kaduna. Both hospitals are located in Kaduna state, North-Western Nigeria and are major referral centers for epilepsy care in Northern Nigeria. Consecutively consenting PWE; of which diagnosis of epilepsy was based on the occurrence of at least two unprovoked seizures 24 hours apart with reliable eye witness account and supportive electroencephalographic (EEG) finding 3. The participants consisted 35 age and sex matched apparently healthy persons with no history of seizures; 35 PWE who were receiving ASM for at least 1 year; and 35 newly diagnosed PWE who were yet to commence ASM (ASM-naïve). All the participants were at least 15 years of age. The healthy controls were recruited from the local communities and were at least 18 years old. Participants who were pregnant, using nutritional supplements suspected to contain selenium were excluded. Socio-demographic and relevant clinical information was obtained followed by physical examination including anthropometry and collection of blood sample for analysis of selenium and glutathione peroxidase.

**2.4 Blood collection, sample preparation and analysis:**

Ten millilitres (10 ml.) of venous blood sample collected from each participant for the determination of concentrations of erythrocyte glutathione peroxidase (GSH-Px) and selenium. GSH-PX was assayed through quantitative colorimetric method using enzyme linked immunosorbent assay (ELISA) kits while selenium was determined using Atomic Absorption Spectroscopy (AAS). The blood was collected into labeled plain vacutainers and allowed to clot at room temperature. The sera then separated into plain centrifuge tubes and centrifuged for 10 minutes at 4,000 revolutions per minute. A portion of the obtained supernatants of each blood sample was kept in labeled plain tubes for GSH-PX and selenium assay. The preparation of the blood samples was done at the Chemical Pathology laboratory of Ahmadu Bello University Teaching Hospital Zaria while selenium analysis was carried out at National Agricultural Research Institute and Technology (NARICT) both in Zaria, Kaduna State Nigeria.

**2.4.1 Erythrocyte** G**lutathione Peroxidase (GSH-Px).** This was determined using the method described by Paglia and Valentine in 1967.16 This method measures the activity of erythrocyte-glutathione peroxidase (GSH-Px). The addition of cumenehydroperoxide in the presence of GSH-Px, glutathione reductase and NADPH causes the oxidation of GSH to glutathione disulphide (GS-SG) and NADP+. Cumenehydroperoxide (10µL) diluted with 10 ml of distilled water was carefully mixed with 50µL of the test sample by shaking. The activity of GSH-Px was determined at a wavelength of 340nm and at 37oC.

**2.4.2 Selenium analysis**

Digestion of a portion (0.1 ml.) of the obtained supernatants of each blood sample was done using 1 ml of concentrated hydrochloric acid (HCl) plus 1ml of concentrated perchloric acid and water (H2O) all made up to 3ml. Analysis of selenium level was done using Atomic Absorption Spectroscopy (AAS) Agilent-240.

**2.5 Statistical Analysis**

Statistical Package for Social Sciences (SPSS) software (version 17; SPSS, Chicago, IL, USA) was used to analyze the data obtained. Quantitative variables such as weight, height, body mass index (BMI), GSH-PX and selenium levels were presented as mean and standard error of mean. The results were presented as tables and charts where necessary. Comparison between the new PWE and follow up PWE was determined by independent samples t -test while correlation analysis was done using Pearson’s correlation. Statistical comparison among the three groups was done by using one-way analysis of variance (ANOVA) followed by Bonferroni post hoc test. Statistical significance was defined as *P* ≤ 0.05.
**3. RESULT:**

**3.1 Socio-Demographic Characteristics of Participants**

The mean age of the controls, follow up PWE and new PWE were 33.31 ± 1.80, 33.91 ± 2.35 and 31.25 ± 2.48 years respectively and there was no significant difference (*P* > 0.05) between them. Table 1 shows the age bracket distribution of the study participants and the mean ±SEM age for each group. There was no significant difference between the mean age of the 3 study groups (*P* ≥ 0.05). The greatest proportion of the control group and patients on follow up were within the age bracket of 26-35 years (28.6% and 37.1% respectively), while more (48.6%) of the newly diagnosed patients was within the age bracket of 15-25 years. The number of participants in the younger age brackets of ≤ 35 years in all 3 groups was more, 23 (65.7%) control, 22 (62.8%) follow ups and 17 (48.6%) new patients.

**Table 1: Age distribution of study participants**

|  |  |  |  |
| --- | --- | --- | --- |
| **Study groups** |  **Frequency of Age brackets** | Age range | Mean ±SEM  |
| 15-25 | 26-35 | 36-45 | 46-55 | 56-65 | ≥66 |
| **Control** | 7(20.0%) | 10(28.6%) | 6(17.1%) | 6(17.1%) | 3(8.6%) | 3(8.6%) | 16-69 | 33.31±1.80 |
| **Follow up** | 9(25.7%) | 13(37.1%) | 8(22.9%) | 1(2.9%) | 3(8.6%) | 1(2.9%) | 15-69 | 33.91±2.35 |
| **New patients** | 17(48.6%) | 6(17.1%) | 5(14.3%) | 5(14.3%) | 1(2.9%) | 1(2.9%) | 15-80 | 31.25±2.48 |

Data expressed as mean ± SEM; n = 35; p > 0.05 using one-way ANOVA; SEM =Standard error of mean

**3.1.1 Marital status:**

Out of the 22 (62.9%) male and 13 (37.1%) female subjects recruited in each study group with male to female ratio of 1.7: 1. About 9 (25.7%) were single, and 26 (74.3%) were married for the control group, while the follow up and newly diagnosed groups had 19 (54.3%) and 18 (51.4%) respectively for single; and married, 16(45.7%) and 17 (48.6%) respectively.

**Figure 1: Distribution of marital status of study groups**

**3.1.2 Educational status of study groups**

For Educational status**,** no formal education is in the ratio of 3 (8.6%), 6 (17.1%) and 9 (25.8%) for control, follow up and newly diagnosed respectively. For primary education, it is 8 (22.9%), 8 (22.9%) and 5 (14.3%); secondary education had 9 (25.7%), 11 (31.4%) and 11 (31.4%), while tertiary education is 15 (42.9%), 10 (28.6) and 10 (28.6)

**Figure 2: Educational status of study groups**

**3.2 Clinical Characteristics of Patients with Epilepsy**

A significant proportion (11.4%) of the follow up PWE had positive family history of seizure disorder as against none (0%) among the new PWE (p = 0.039). Also, a significant proportion of the follow up PWE had illness duration of **≤** 10 years compared to the new PWE (P = 0.012). Regarding number of seizure frequency per month, a significant proportion of the follow up PWE had 0-2 seizures per month (p = 0.001) as against those with 3-5 seizures per month. Other details are shown in Table 2 below. Among the follow up PWE on ASM; 26 (74.3%) were on Carbamazepine and 9 (25.7%) were on Sodium valproate.

**Table 2 Clinical Characteristics of Patients with Epilepsy**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristics of Seizure** | **Follow up****Number (%)** | **New patients** **Number (%)** |  **p-value** |
| **Seizure Type** |  |  |  |
| Focal |  22 (62.9) | 17 (48.6) |  0.229 |
| Generalized | 13 (37.1) | 18 (51.4) |  |
| **Family History of Seizure** |  |  |  |
| Present | 4 (11.4) | 0 (0.0) | 0.039\* |
| Absent | 31 (88.6) |  35 (100.0) |  |
| **Age at onset of Illness in Years** |  |  |  |
| **≤** 30 Years | 30 (85.7) |  25 (71.4) | 0.145 |
| **≥** 31 Years | 5 (14.3) |  10 (28.6) |  |
| **Duration of Illness in Years** |  |  |  |
| **≤** 10 Years | 18 (51.4) |  28 (80.0) | 0.012\* |
| **≥** 11 Years | 17 (48.6) |  7 (20.0) |  |
| **Seizure Frequency Per Month** |  |  |  |
| 0-2 |  29 (82.9) | 16 (45.7) | 0.001\* |
| 3-5 |  6 (17.1) | 19 (54.3) |  |

**3.3 Anthropometry of study participants**

The mean weights of the subjects were 64.55±2.29, 61.54±2.45 and 58.32±2.69 respectively for the controls, follow up and new patients. The mean heights were 1.64±0.01, 1.65±0.01 and 1.60±0.01. Mean body mass index (BMI) of 23.88±0.84, 22.29±0.73 and 22.51±0.76 was also obtained; and there was no significant difference between the study groups (*P* ≥0.05) Table 3.

**Table 3: Anthropometric Measurement of Participants**

|  |  |
| --- | --- |
| **Study group** |  **Mean ± SEM** |
| **Weight (Kg)** | **Height (M)** | **BMI (Kg/M2)** |
| **Control** | 6 4.55 ± 2.29 |  1.64 ± 0.01 | 23.88 ± 0.84 |
| **Follow up** | 61.54 ± 2.45 |  1.65 ± 0.01 | 22.29 ± 0.73 |
| **New patients** | 58.32 ± 2.69 | 1.60 ± 0.01 | 22.51 ± 0.76 |

**3.4 Selenium and Glutathione Peroxidase Level**

There was significant difference (*P* = 0.000) in the mean serum selenium level among the three groups. The selenium level in the follow up group was significantly higher than the new patients (*P* = 0.001) and the controls (*P* = 0.000) but there was no significant difference between the selenium levels in the new patients and controls (*P* = 1.000). The follow up group had significantly lower level of glutathione peroxidase compared to the new patients and control group (*P* = 0.000) in each instance. The new patients have significantly lower level of glutathione peroxidase compared to the control group (*P* = 0.11). Also, selenium correlated significantly negatively with GPX (r = - 0.289, *P* = 0.003).

**Table 4: Selenium and Glutathione Peroxidase Levels in Participants**

|  |  |  |
| --- | --- | --- |
| **Participants** |  **Selenium (ng/L)** **Mean ± SEM** | **Glutathione Peroxidase (µ/L) Mean ± SEM** |
| Control | 0.208 ± 0.006\* | 51.25 ± 0.66\* |
| Follow up | 0.246 ± 0.005\*\* | 45.80 ±0.73\*\* |
| New Patients | 0.214 ± 0.005\* | 48.48 ±0.56\*\* |

Data expressed as mean ± SEM; n = 35; \* = *P* < 0.05 using one-way ANOVA followed by Bonferonni post hoc test which compared follow up with control and new patients; \*\* = *P* < 0.05 using one-way ANOVA followed by Bonferonni post hoc test which compared new patients with controls.

**3.5 Relationship between Participants Characteristics, Selenium and Glutathione Peroxidase**

In the patients on follow, their BMI correlated significantly positively with their age, r = 0.375, *P* = 0.041. Also, their age correlated significantly positively with the age at onset of epilepsy r = 0.786, *P* = 0.000.

Among the new patients, their BMI correlated significantly positively with their age, r = 0.547, *P* = 0.001 and age at onset of epilepsy. Equally, their age correlated significantly positively with the age at onset of epilepsy r = 0.826, *P* = 0.000.

However, there was no significant relationship between selenium and glutathione levels with participants clinical characteristics such as seizure type, seizure frequency, age at onset of epilepsy and duration of epilepsy *P* > 0.05.

1. **DISCUSSION:**

 Epilepsy is a common chronic neurological disorder that is of public health concern. Our study revealed that majority of the patients were in the 26-35 age range. This aligns with the finding of some previous researchers.17,18. The high prevalence of epilepsy among the productive and active age group could be related to the common risk factors for the disease such as head injury and central nervous system infections like meningitis, encephalitis which is rampant in the region.19. This study also showed a male preponderance as has been documented in previous studies.17,18, 20. Some of the reasons that could be attributed for this may include the patriarchal nature of the African society, the males could seek medical help on their own while the female folks must get the husband or father’s permission before they can go to the hospital.20

In general, out of the 70 patients in this study (both follow up and new), 39 (55.7%) had partial (focal) seizure, while 31 (44.3%) patients had generalized seizure. Such variation in seizure types was also noted in the study of other investigators.17,21,22 This is particularly so if the seizure classification was done based on EEG finding as in the present study. When eye witness account only is used, some patients with a focal with secondarily generalized seizures (focal to bilateral tonic-clonic seizures) could be misclassified as generalized seizures.23

Antiseizure medications (ASM) are the mainstay of epilepsy treatment, they are used to reduce the frequency of the seizure but they do not produce curative effect (anti-epileptogenic).24 In this study, the effect of ASM was clearly reflected as majority, (82.9%) of the follow up PWE had none to two episodes of seizure in the preceding four weeks. This indicates that with regular ASMs use, patients can achieve relatively good seizure remission.However**,** sometimes the seizures and indeed the disease may be refractory to many of the available ASM which has been described as drug resistant (refractory) epilepsy.25

Some Studies have suggested a relationship between the level of selenium in PWE and drug-resistant (refractory) epilepsy. They reported that lower levels of selenium have been implicated in drug-resistant epilepsy.26,27 The present study compared the levels of selenium and gluthathione peroxidase among healthy controls; ASM-experienced PWE and ASM-naïve PWE. We found that the serum selenium levels in the follow up group (ASM-experienced PWE) was significantly higher compared to the new patients (ASM-naïve PWE). Equally, the serum selenium levels of the follow up group (ASM-experienced PWE) was significantly higher than the controls; while there was no significant difference in the serum selenium levels between the new patients and controls. The finding from the present study is in contrast to a study by Nisar et al in Pakistan among ASM-naïve patients with idiopathic generalized epilepsy which reported significantly lower selenium levels compared to healthy controls. 18 Also, contrary to our study finding, Jia et al in a systematic review and meta-analysis had revealed significantly lower serum selenium in ASM-experienced PWE in comparison with healthy controls.28

Selenium is an essential micronutrient for antioxidant defense that integrates an important part of selenoproteins. Selenium is vital for the central nervous system and it is involved in various functions. This important antioxidant plays a role in the reduction of hydrogen peroxide, deleterious lipid and phospholipid hydroperoxides in the brain to harmless bye-products. Hence, it has been postulated that the lower levels of selenium among PWE could be linked with its utilization in reducing the free radicals produced during seizure episodes.11

Our study also found that the follow up group (ASM- experienced PWE) had significantly lower level of glutathione peroxidase compared to the new patients (ASM-naïve) and control groups. Also, the new patients (ASM-naïve PWE) have significantly lower levels of glutathione peroxidase compared to the control group (healthy persons). The present result aligns with the study by Hamed et al in Egypt that showed significantly lower levels of GPX in the new patients, yet to commence ASM in comparison to healthy controls.29 Also, our current finding was almost similar with the study by Nisar et al in Pakistan except that they showed non- significant lower serum levels of GPX in PWE compared to the healthy group.18 A meta-analysis on glutathione peroxidase in patients with epilepsy showed that there was no significant difference in GSH-Px levels between PWE and healthy controls.30

Our study found that Selenium correlated significantly negatively with GPX. Therefore, it is suggested that supplementation of selenium (which is a major cofactor for GSH-Px) could be beneficial in cases of depletion of this microelement in PWE. Assessment of GSH-Px level has been described as an essential diagnostic marker of resistant epilepsy 31

This study did not observe any significant difference in body mass index (BMI) between the healthy controls, follow up (ASM – experienced) PWE and the newly diagnosed (ASM-naïve). This was equally the same for the ASM- naïve and the control group. Similar findings have been reported by Ogunro *et al*. 32 Contrary to this, Amer et al in Zazazig University Hospitals, Egypt reported significantly higher BMI among PWE on ASM than the healthy group.33

Finally, there was no significant relationship between selenium and glutathione levels with participants clinical characteristics such as seizure type, seizure frequency, age at onset of epilepsy and duration of epilepsy. This is in agreement with the study by Nisar et al except that for the seizure frequency, GPx1 levels were significantly lower in patients having more than five seizure attacks.18

**4.1 Strength and Limitation:**

We compared the levels of selenium and gluthathione peroxidase among healthy controls; ASM-experienced PWE and ASM-naïve PWE. The inclusion of ASM-naive patients gives credence to this study as it removes the possibility of the confounding influence of ASMs which could affect the selenium and gluthathione peroxidase levels and subsequently the antioxidant defense system. This has enhanced the reliability of our result as the noticed changes in these parameters could be attributable to the influence of epilepsy. However, a larger sample size of patients from various regions will be necessary to be able to generalize these findings.

**4.2 Conclusion:**

We found selenium level in the follow up group (ASM – experienced) to be significantly higher than the new patients (ASM- naïve) and the healthy controls with no significant difference between the ASM-naïve and healthy controls. Selenium correlated significantly negatively with glutathione as the ASM – experienced PWE had significantly lower level of glutathione peroxidase compared to the ASM - naive and healthy controls. Also, ASM- naïve PWE have significantly lower level of glutathione peroxidase compared to the healthy controls.

**CONSENT**

Informed consent was obtained from all the participants in this study.

**ETHICAL APPROVAL**

Ethical approval was obtained from Health Research Ethical Committee (HREC) of the two institutions used before commencement of the study.

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