

**A COMPARATIVE STUDY OF TESTOSTERONE,SEX HORMONE
BINDING GLOBULIN AND FREE ANDROGEN INDEX LEVELS IN
MEN WITH EPILEPSY AT KENYATTA NATIONAL HOSPITAL
NEUROLOGY CLINIC**

BY

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**A dissertation submitted in part fulfillment of the award of Master of Medicine in Internal
Medicine at the University of Nairobi**

DECLARATION

I certify that this dissertation is my original work and has not been presented for a degree in any other university.

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DEDICATION

I dedicate this study to my loving wife Rosetta and my two lovely boys Evans and Felix for their sacrifice and unwavering support during my study.

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Special thanks to my supervisors, Prof. Adam, Prof. Amayo and Prof. Kigonde for their guidance and support.

Secondly I want to acknowledge and thank the management and staff of KK SHAH LABORATORIES for their valuable services.

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ABBREVIATIONS

AEDs	Anti-epileptic drugs.
BAT	Biologically Active Testosterone.
CBZ	Carbamazepine
CRH	Cortisol Releasing Hormone
DHEAS	Dihydroepiandrosterone
E2	Estradiol
EIAEDs	Enzyme Inducing Anti-Epileptic Drugs.
FAI	Free Androgen Index.
FSH	Follicle Stimulating Hormone.
FT	Free testosterone.
GABA	Gamma Aminobutyric Acid
GALP	Galanin –like Peptide.
GnRH	Gonadotrophin Releasing Hormone
KNH	Kenyatta National Hospital.
LH	luteinizing Hormone.
MWE	Men with Epilepsy.
NE	Norepinephrine.
NYP	Neuropeptide Y
PHT	Phenytoin.
PRL	Prolactin.

SHBG	Sex Hormone Binding Globulin.
SDI	Sexual Desire Inventory.
SRI	sexual response inventory
TLE	Temporal lobe Epilepsy
TT	Total Testosterone
LRE	Localization Related Epilepsy
VPA	Valproate.

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ABSTRACT

Background; Epilepsy, anti-epileptic drugs and the reproductive system have complex interactions. Reproductive endocrine disorders are more common among patients with epilepsy than in the general population. These disorders have been attributed to both epilepsy and the anti-epileptic drugs. Use of anti-epileptic drugs especially the enzyme inducing drugs increases hepatic synthesis of Sex Hormone Binding Globulin in both men and women.

The increase in Sex Hormone Binding Globulin level leads to increased binding of testosterone effectively reducing the fraction of biologically active testosterone available for tissue binding and action. This may have effects on sexual function and fertility of affected individuals.

Broad objective; To assess the effects of Anti-Epileptic drugs on male reproductive hormones in male patients attending neurology clinic at Kenyatta National Hospital.

Study design: Cross sectional comparative survey.

Study population: Sixty three (63) adult male epileptic patients attending neurology clinic at Kenyatta National Hospital. A comparative group of sixty three (63) healthy adult males accompanying patients to outpatient clinics.

Study setting: This study was carried out at the neurology clinic. Participants in the comparative group were recruited from medical, surgical outpatient clinics, Accident and Emergency department of KNH.

Methods: Patients and age matched comparative cases were consecutively sampled. A venous blood sample for determination of total testosterone levels and Sex Hormone Binding Globulins levels was drawn. Free androgen Index was calculated for all study cases and the comparative group.

Results: The mean testosterone levels was found to be higher in the study group compared to the comparative group (22.1 ± 8.2 nmol/l versus 15.3 ± 8.2 nmol/, $p < 0.001$), this difference was statistically significant. The study group had higher mean levels of Sex Hormone binding Globulin compared to the comparative group, the difference achieving statistical significance (62.9 ± 27 nmol/l versus 44.6 ± 26.7 nmol/l, $p < 0.001$). The Free Androgen Index was

comparable in the two groups with no statistically significant difference(38.4 ± 14.4 versus 38.9 ± 18.7 , $p=0.873$).

Conclusion: This study showed that men with epilepsy on Anti-epileptic drugs had higher concentrations of both Total Testosterone and Sex Hormone Binding Globulin than normal healthy aged matched men. However Free Androgen Index was not reduced in the male patients compared to the comparative group.

1.0 LITERATURE REVIEW

1.1 INTRODUCTION

Epilepsy is a chronic disorder characterized by recurrent seizures which may vary from brief lapse of attention or muscle jerks to prolonged convulsions. Seizure is a paroxysmal event due to abnormal discharge from an aggregate of neurons in the brain. Epilepsy is defined as two or more unprovoked seizures[1]. It's a chronic condition requiring long term therapy with Anti-epileptic drugs. Some of the Anti-epileptic drugs have side effects that may have long term psychosocial effects on health of people living with epilepsy.

Association between epilepsy and reproductive disorders were first described in the 1950's by Gaustat and Collomb[2] who studied sexual behavior in 36 cases of psychomotor seizure, hypo sexuality was found in twenty six(26) of the patients. Patients had profound decrease in libido, decrease in sexual curiosity and lack of desire for sexual intercourse.

Blumer and Walker (1967)[3] studied 21 patients with Temporal lobe epilepsy. Eleven(11) patients were found to have global hypo sexuality pre-operatively. Following lobectomy sexuality returned in proportion to degree of seizure control.

Shukla et al (1979)[4] compared sexual functioning between patients with Temporal lobe epilepsy and generalized epilepsy. Fourty four patients, 30 males and 14 females with temporal lobe epilepsy were included into the study, their sexual functioning was compared to that of fortyseven(47) patients, 34 males and 13 females with generalized epilepsy. Sexual functioning in each group was established through interviews. In each gender, hyposexuality was more common in the temporal epilepsy group compared to the generalized epilepsy group.

Further evidence of the complex interaction between epilepsy and sexual dysfunction was demonstrated by a study done by Hamed et al(2006)[5] in Egypt. 44 men with generalized epilepsy aged between 18-48 years were studied. Sexological and psychological interviews together with serum total testosterone, estradiol, Luteinizing Hormone, Follicle Stimulating Hormone and prolactin levels were determined. Hyposexuality was found in 61.4% of the patients with erectile dysfunction and premature ejaculation being found in 70.4% and 66.7% of the patients respectively. Total testosterone remained within the normal range for all patients but

was significantly lower in the hyposexual patients compared to the non-hyposexual patients ($p < 0.02$).

Toone et al (1989) [6] was also able to demonstrate the interaction between sexual disturbance, epilepsy and hormonal disturbance in epileptic patients. They studied 54 men undergoing treatment for epilepsy. A detailed inquiry of their sexual activity and behavior was made. Anterior pituitary and sex hormones were also measured. Low levels of sexual interest and activity was demonstrated in the patients. Those with focal epilepsy were found to be more impaired in their sexual functioning compared to those with generalized epilepsy. Plasma free testosterone was reduced in the patients compared to the healthy comparative group. However Sex Hormone Binding Globulin, Luteinizing Hormone, Follicle Stimulating Hormone levels were increased in the patients compared to the healthy comparative group.

Anti-epileptic drugs are known to induce reproductive endocrine disorders. Dana-Haeri et al (1982) [7] were the first to objectively measure sex hormones in epileptic patients on AEDs. They studied 37 male epileptic patients aged 17-40 years on one or more of the following AEDs; Carbamazepine, Phenytoin, Primidone and sodium valproate attending epilepsy centre at national hospital in England. Levels of Sex Hormone Binding Globulin, Total Testosterone, Free Androgen Index were measured and findings compared to 16 healthy volunteers aged 19-40 years. SHBG levels were found to be significantly higher in patients than in comparative group [49 nmol/l (10-106) versus 23.3 nmol/l (19-28) $p < 0.001$]. Total testosterone levels remained within normal range for both groups [23.3 nmol (13.0-46.9) versus 21.0 nmol (14.1 -25.5)]. Free Androgen Index was found to be significantly reduced in the patient group compared to comparative group [0.35 (0.15-0.89) versus 0.55 (0.40-0.74)]

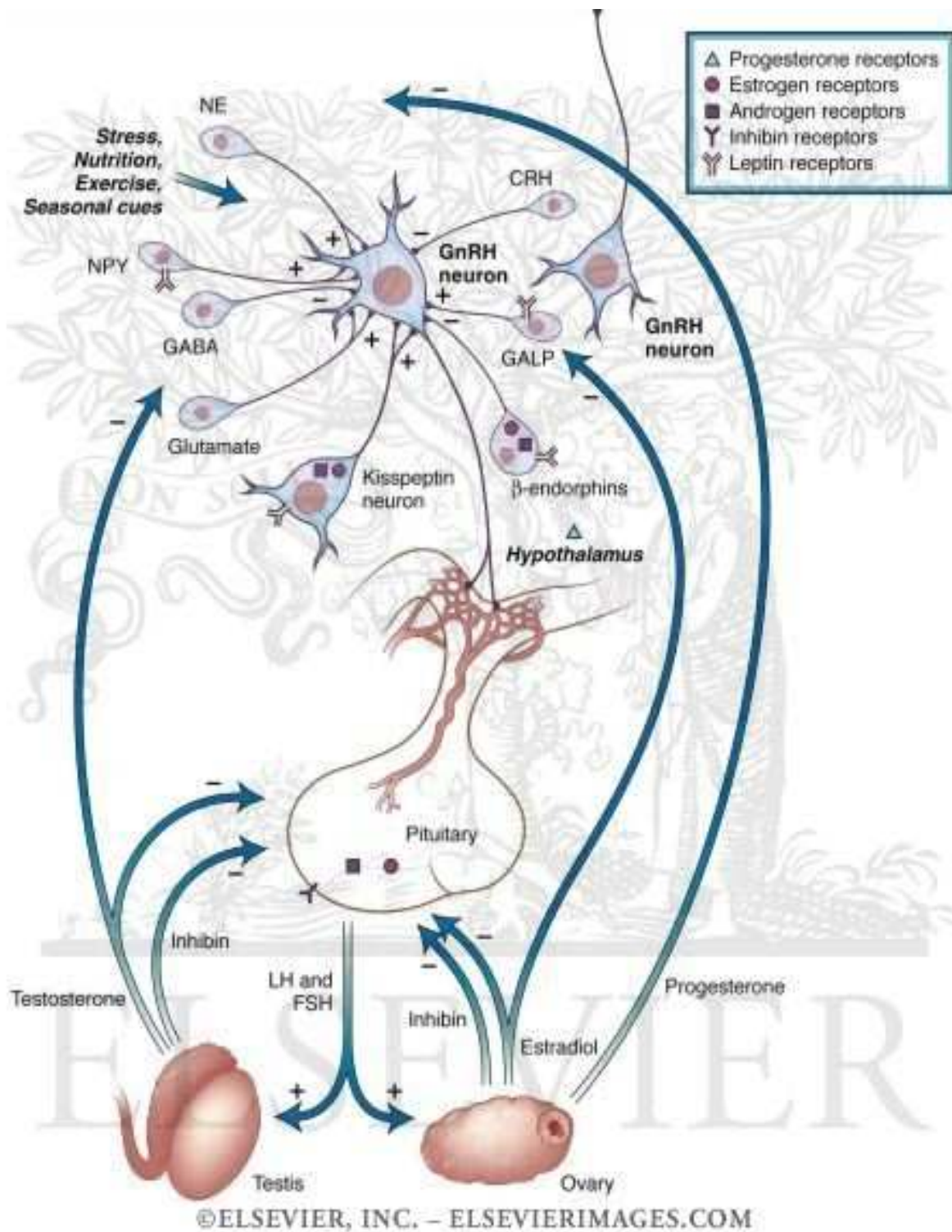
1.2 EPIDEMIOLOGY

Epilepsy has a worldwide distribution with a greatly varying prevalence. Prevalence has been estimated at 5-10 persons per 1000 population. However marked variation in prevalence have been noted in different locations around the globe [8,9,10,11 ,12].

1.3 REPRODUCTIVE HEALTH UNIT

Hypothalamus is the integrating centre of the reproductive hormonal axis. It's the site of production of peptide hormone, Gonadotrophin releasing hormone (GnRH) which is transported to the adenohypophysis of the pituitary gland. GnRH stimulates synthesis and release of gonadotrophin hormones, lutenizing hormone (LH) and follicle stimulating hormone(FSH).

Both neural input from the central nervous system and humoral factors from the testis modulate secretion of GnRH. Release of GnRH is seasonal, peaks in spring, circadian (highest in the morning) and pulsatile (peaks after every 90-120 minutes).



The diagram demonstrates the complex interaction between neural, environmental and humoral factors in influencing the hypo-thalamo-pituitary-gonadal axis and the negative feedback effects of the sexual hormones on the hypothalamus and pituitary.

Figure 1: Reproductive endocrine unit

1.4 TESTOSTERONE

Testosterone exists in three(3) principal forms;

- Tightly bound to SHBG -45-50%.
- Loosely bound to Albumin 50-55%.
- Unbound testosterone 1-2%.

Unbound testosterone comprise the clinically important Biologically Active Testosterone (BAT) whereas SHBG bound testosterone is not available for biological action.

Testosterone reference range-(5.74 nmol/l-30.34 nmol/l). This is the reference range for the kits and method used to measure total testosterone levels for this study.(Appendix5)

1.5 SEX HORMONE BINDING GLOBULIN

SHBG transports androgens and estrogens in blood in blood and regulates their access to target tissues. Hepatic production of SHBG fluctuates throughout the life cycle and is influenced by metabolic and hormonal factors. Some differences are attributable to variations in endocrine and metabolic state. Increased levels may be seen in liverdisease, hyperthyroidism, anorexia, estrogen use and hypogonadism. Decrease in SHBG levels may be seen in obesity, polycystic ovarian syndrome, hypothyroidism, androgen use and Cushing's disease.

Sex hormone binding globulin reference range (17.1 nmol/l-77.6 nmol/l). This is the reference range for the kits and method used to measure Sex Hormone Binding Globulin levels for this study.(Appendix 6)

1.6 FREE ANDROGEN INDEX

True androgen status can be assessed either by measuring free testosterone or by calculating the ratio of the total testosterone (TT) concentration to the concentration of SHBG. This ratio is referred to as free androgen index (FAI). It's calculated on a molar/molar basis .FAI=TT(nmol/l)/SHBG (nmol/l) multiplied by 100.

The FAI is often increased in severe acne,male androgenic alopecia (balding), hirsutism and other conditions in which normal total testosterone level is found with a low SHBG level.

1.7 EPILEPSY AND REPRODUCTIVE HEALTH

Epilepsy, AEDs and the reproductive system have complex interactions. Reproductive endocrine disorders are more common among patients with epilepsy than among the general population. These disorders have been attributed to both epilepsy itself and the AEDs. Use of AEDs especially enzyme inducing AEDs increases hepatic synthesis of SHBG in both men and women. Overtime the increase in serum SHBG levels lead to diminished bioavailability of testosterone resulting in diminished potency and fertility in men.

First reports of these interactions were done in 1954 by Gaustat and Collomb[2] who reported hyposexuality in 26 out of 36 with psychomotor seizures. Patient had profound disinterest in matters of libido with decreased or absent sexual curiosity and lack of desire for sexual contact.

Further evidence of interaction between epilepsy and reproductive dysfunction was demonstrated by Blumer and Walker in 1967 [3], studied 21 patients who had unilateral Temporal Lobe Epilepsy(TLE).Eleven(11) were found to be globally hypo sexual pre-operatively,the outcome following surgery was that sexuality returned in proportion to degree of seizure control.

However, the information in these earlier studies was based on interviews only; no objective measure of sex hormones had been done. First studies reporting reproductive endocrine abnormalities in men taking AEDs and associating them with sexual dysfunction were published in 1970's and 1980's. The consistent finding in these studies was an increase in levels of SHBG which binds testosterone in circulation. Whereas total testosterone levels may be elevated or normal, low levels of bioactive androgens seemed to be associated with diminished sexual function.

Rodin et al [13] 1984 studied effects of epilepsy on sex hormones in 33 patients with epilepsy not on AEDs and compared this to 11 age matched controls. Patients had significantly higher mean levels of LH,FSH,LH,PRL compared to the controls. Total testosterone was reduced,however this was not statically significant. Patients who reported difficulties in sexual arousal had significantly lower levels of testosterone than those who did not. (5.5 ng/ml versus 4.2 ng/ml $P<0.049$).

Herzog et al [14],1986,studied twenty(20) patients referred for neurological evaluation for TLE and found to have diminished sexual interest as per bloomer tool. Reproductive dysfunction included impotence, patient had morning measurement of LH,FSH,TT,PRL and FT and compared to eight(8) matched controls who had normal sexual interest and reproductive function. Eleven (11) had reduced sexual interest and potency. Five (5) patients had abnormally low serum TT,LH or FT .

Isojarvi et al [15] 1995, studied twenty one (21) patients with epilepsy on PHT and CBZ , the patients were prospectively followed up for five(5) years. Eleven were able to complete the five year follow up. Serum TT did not change during CBZ treatment, serum SHBG levels increased and FAI were reduced during the five years of CBZ therapy. Increased serum SHBG and low FAI was observed in patients treated for more than five years. A positive correlation was found between serum SHBG levels and duration of treatment($r=0.605.P<0.05$). Serum SHBG levels were also found elevated, low levels of FAI were found in 88% of patients on long term treatment with PHT. Mean serum testosterone levels were increased in patients receiving PHT, however neither TT or SHBG levels correlated with duration of therapy in patients receiving PHT. SHBG progressively increased with increasing duration of treatment with CBZ with TT remaining unchanged hence the continuously decreasing FAI.

Isojarvi et al [16], 1989, prospectively followed up twenty one (21) with epilepsy on CBZ treatment to establish the effect of duration of therapy on hormone levels.Levels of FT, SHBG, E2,LH ,FSH and FAI were determined before and after two(2) months of carbamazepine treatment. Baseline serum hormones and FAI were calculated in sixteen (16) age matched controls. E2 levels were higher in patients before CBZ treatment than in controls. FAI values and DHEAS levels in patients decreased during the two (2) month treatment with CBZ. Levels of LH ,FSH,TT, FT and SHBG remained unchanged in the two month period.

Talbot et al [17],2008, studied sixty(60) Men with epilepsy on one AED only and compared their sexual functioning and sex hormones to sixty(60) control men. TT, FT, BAT, DHEAs, SHBG were measured in both study subjects and controls. Sexual functioning was evaluated using validated questionnaires (sexual desire inventory SDI sexual response inventory SRI, erectile function, sexual efficacy scale SSE and anxiety and depression scale). Men with epilepsy reported lower levels of sexual desires and, depression and psychological stress. Men with

epilepsy had higher levels of SHBG and significantly lower levels of DHEAs. However there were no significant differences between the groups' levels of TT, FT, and BAT. BAT levels were significantly lower in men taking EIAEDs than those taking non-enzyme inducing AEDs.

Herzog et al [18], 2004, compared sexual function and reproductive hormone levels among men with localization-Related Epilepsy(LRE) on various anti-epileptics and normal controls. Sixty three(63) men with LRE ,thirty six(36) on EIAEDs ,Eighteen(18) on lamotrigine, nine(9) not on any AEDs and eighteen(18) normal controls. Sexual function and interest using S-scores and levels of BAT, BAE, SHBG and BAT/BAE ratio were compared among the groups. BAT/BAE levels were significantly lower in the EIAEDs group than in the normal control and lamotrigine groups. SHBG levels were significantly higher in the EIAEDs group than all other groups. Men with LRE had abnormal low levels of S-scores than those in the other groups(33.3% on EIAEDs,5.5% in those taking lamotrigine and 22.2% in those not on AEDs).BAT was low in 55.6% in those taking EIAEDs compared to 33.3% in those taking lamotrigine and 33.3% in those not on any AEDs .Among men with low S-scores ,86.7% had low levels of BAT compared to 33.3% with normal S-scores($P<0.01$).This led to conclusion that sexual function ,BAT,BAE, levels were higher in the lamotrigine group than in patients taking EIAEDs. S-score is a score derived from a forty six(46) item self administered tool used for assessment of sexual functioning.

Barragry J M et al[19],1978,measured SHBG and TT levels in twenty nine(29) patients,(16 men and 13 women) with epilepsy on chronic therapy with AEDs.TT levels were significantly higher in those receiving AEDs than in the male unmedicated control group(30 ± 17.1 nmol/l versus 16 ± 3.7 nmol/l $P<0.02$).The plasma SHBG levels was greater in males with epilepsy than for the male control group(7.3 ± 1.4 versus 5.76 ± 0.82 , $P<0.01$).

2.0 STUDY JUSTIFICATION

Epilepsy is a common problem associated with long term use of AEDs, some with adverse effects which may have adverse effects on the reproductive health of men with epilepsy. These effects may negatively affect the psychosocial well being of the patients .Some of these effects may also affect the sexual relationship between the patients and their spouses.

There is absence of local studies on the effects of long term use of AEDs on the reproductive hormone status of men with epilepsy on Anti-epileptic drugs. There are no studies done locally to compare the effects of the traditional Enzyme Inducing Anti-epileptic drugs against the newer drugs which are mainly non enzyme inducing AEDS.

The finding of this study may provide room for intervention in terms of advice on choice of AEDS (enzyme inducers versus non enzyme inducing AEDs).

The study aims to establish the baseline data on the testosterone status of men with epilepsy in Kenyatta National Hospital.

3.0 RESEARCH QUESTION

What are the levels of testosterone, Sex Hormone Binding and Free Androgen Index in male epileptic patients attending neurology clinic at Kenyatta National Hospital.

4.0 BROAD OBJECTIVE

To assess the levels of male reproductive hormones in male patients with epilepsy attending Neurology clinic at KNH.

4.1 Primary Objectives

1. To determine and compare the levels of total testosterone in male patients with epilepsy on AEDS and a comparative group in KNH.

2. To determine and compare the level of SHBG in male patients with epilepsy on AEDs and in the comparative group in KNH.
3. To determine and compare the FAI in both patients and the comparative group.

4.2 Secondary objective

1. To determine the effects of duration of therapy of AEDs on levels of total testosterone in men with epilepsy.
2. To determine the effects of duration of therapy of AEDs on the levels of Sex Hormone Binding Globulin in men with epilepsy.
3. To compare the effects of enzyme inducing anti-epileptics versus Non Enzyme inducing drugs on the levels Total testosterone and Sex Hormone Binding Globulin in men with epilepsy on AEDS.

5.0 METHODOLOGY

5.1 STUDY DESIGN

This study was a cross sectional comparative survey.

5.2 STUDY SITE

Kenyatta National Hospital neurology clinic, medical and surgical outpatient clinics, Accident and emergency department.

5.3 STUDY PERIOD

The study was carried out once weekly at the neurology clinic where the study group participants were recruited. The participants in the comparative group were recruited daily from outpatient clinics and the emergency and Accident department, between the February 2013 and April 2013.

5.4 STUDY POPULATION

The study population consisted of Epileptic patients on AEDs on follow up at the neurology clinic, Kenyatta National Hospital. The participants in the comparative group were age matched healthy males accompanying patients to the outpatient clinics and Accident and Emergency departments.

5.5 STUDY SUBJECTS

5.5.1 Inclusion criteria

1. Men with epilepsy aged 18-50years.
2. Duration of therapy of AEDS of six months or more.
3. Those who give written informed consent.

5.5.2 Exclusion criteria

1. Patients with documented or suspected liver/thyroid or renal disease.
2. Patients with orchidectomy or gonadal irradiation.
3. Patients with suspected or documented hypogonadism.
4. Patient who decline to give informed consent.
5. Patients on hormone replacement.

5.6 COMPARATIVE GROUP

5.6.1 Inclusion criteria

1. Men aged 18-50years.
2. Those who gave informed consent.

5.6.2 Exclusion criteria

1. Men with documented or suspected liver/thyroid or renal disease.
2. Men with orchidectomy or gonadal irradiation.
3. Men with suspected or documented hypogonadism.
4. Men who decline to give informed consent.
5. Men on hormone replacement.

5.7 STUDY VARIABLES

Demographic data

- Age
- Marital status
- Education level.
- Employment

Clinical data

- Seizure type
- Type, dosage and number of AEDS used.
- Duration of AEDs therapy.

Laboratory data

- Total testosterone levels.
- SHBG levels
- Calculated FAI

5.8 SAMPLE SIZE CALCULATION

The sample size for this study will be calculated as follow;

N=sample size, 60

$$Z_{1-\alpha/2}^2 P (1-P)$$

N=

$$d^2$$

- N=sample size.
- $Z_{1-\frac{\alpha}{2}}$ Two sided significance level of significance $(1-\alpha)$ -95%=1.96.
- P=estimated proportion of epileptic patients on AEDs with reduced levels of free androgen index(11%).This is from a study done by Kuba et al[20] who found 11% of their study subjects had reduced free androgen index.
- d=precision error= $\pm 5\%$

The required sample size was 60.

5.9 SAMPLING METHOD

Consecutive sampling was used to recruit both study patients and comparative group subjects.

5.10 PATIENTS SELECTION AND RECRUITMENT

Patient screening was done by the principal investigator using information on the files to determine those who met the inclusion criteria. The information sought from patients files included information on seizure type, drug type, dosage and duration of therapy. Baseline results on renal and liver function tests were perused and those patients found to have deranged renal and liver function tests excluded. However thyroid function tests were not available as this test is not routinely done in our patients. Patients found to meet inclusion criteria were then called individually to consultation room for counseling and explanation of study procedure. Signed informed consent was obtained from the patient, following a thorough explanation of the study by the principal investigator. A trained research assistant who was a qualified clinical officer was used to collect blood from the selected study participants.

A standard questionnaire was administered by the principal investigator covering the demographic and clinical data on the patients.

A physical examination was conducted by the principal investigator looking for signs of liver disease, goiter, evidence of renal disease and secondary sexual characteristics.

The comparative group subjects were recruited from a population of male relatives accompanying patients to various outpatient clinics and the Accident and Emergency department of Kenyatta National Hospital. The comparative group was age matched to the study subject's ± 5 years. The comparative group subjects were recruited during the subsequent days after recruitment of the study group to enable the process of age-matching.

A 5ml sample of blood was collected aseptically from the antecubital fossa into a plain vacutainer tube labeled appropriately and sent for TT and SHBG Levels measurement. Specimen collection was done between 9.00AM -11.00 AM by the principal investigator and a trained research assistant. Blood samples were centrifuged for 20 minutes ,serum separated and sample frozen at -20 °C until total testosterone and Sex Hormone Binding Globulin levels were

measured .The timing of sample collection was similar for both study participants and the comparative group participants. This was also important to minimise changes in testosterone levels that may be caused by circadian /pulsatile nature of testosterone release.

5.11 LABORATORY PROCEDURES

Total Testosterone levels were measured using ARCHITECT assay, a chemiluminescent micro particle immunoassay. SHBG levels were measured using a two step immunoassay using the chemiluminescent micro particle immunoassay. Details of the specific laboratory procedures are attached as appendix 4 and 5.

5.12 QUALITY CONTROL

Strict adherence as per the manufacturer's manuals for both tests was observed. All the tests were run as a single batch to minimize intra user variability.

5.13 DATA MANAGEMENT AND ANALYSIS

Data was collected and entered into a study profoma. Data from questionnaire was coded and entered and managed in a predesigned Microsoft database. Data entry was done continuously during course of data collection. At end of data entry, data was cleaned and analyzed using SPSS version 18.0.

Socio-demographic characteristics of the study population were summarized into means and standard deviations for age and proportions for categorical variables such as education, employment and marital status. The characteristics were compared between the cases and comparison group using chi square test for categorical data and Student's t test for mean age.

The levels of total testosterone, Sex Hormone Binding Globulin and Free Androgen Index were presented as means and standard deviations. Testosterone, SHBG and free androgen index levels were compared between study population and comparative group using student's t-test. Also, the associations of testosterone, SHBG and free androgen index levels with the number of drugs were tested using ANOVA test. Linear regression was performed to determine the association between duration of therapy and the hormones (testosterone and SHBG).

All statistical tests were performed at 5% level of significance (95% confidence interval).Study findings are presented using tables, figures and graphs).

6.0 ETHICAL CONSIDERATION

Permission to carry out the study was sought from the Kenyatta hospital /university of Nairobi scientific and Ethical Review committee. Study participants were enrolled after thorough counseling and subsequent informed consent dully signed. Patient confidentiality was maintained at all times. There was no discrimination to any patient who declined enrollment. Patient usual care was not interrupted.Finding of study was shared with the study subjects and relevant care givers.

7.0 RESULTS

A total of 68 study participants were recruited into the study. Sixty three (63) were analyzed with two declining consent, two others had post brain surgery seizures hence excluded with one blood sample reported to have hemolysed unfit for analysis. A total of 63 age matched participants were recruited into the study and all were analysed.

Figure 2: Flow chart of recruitment process

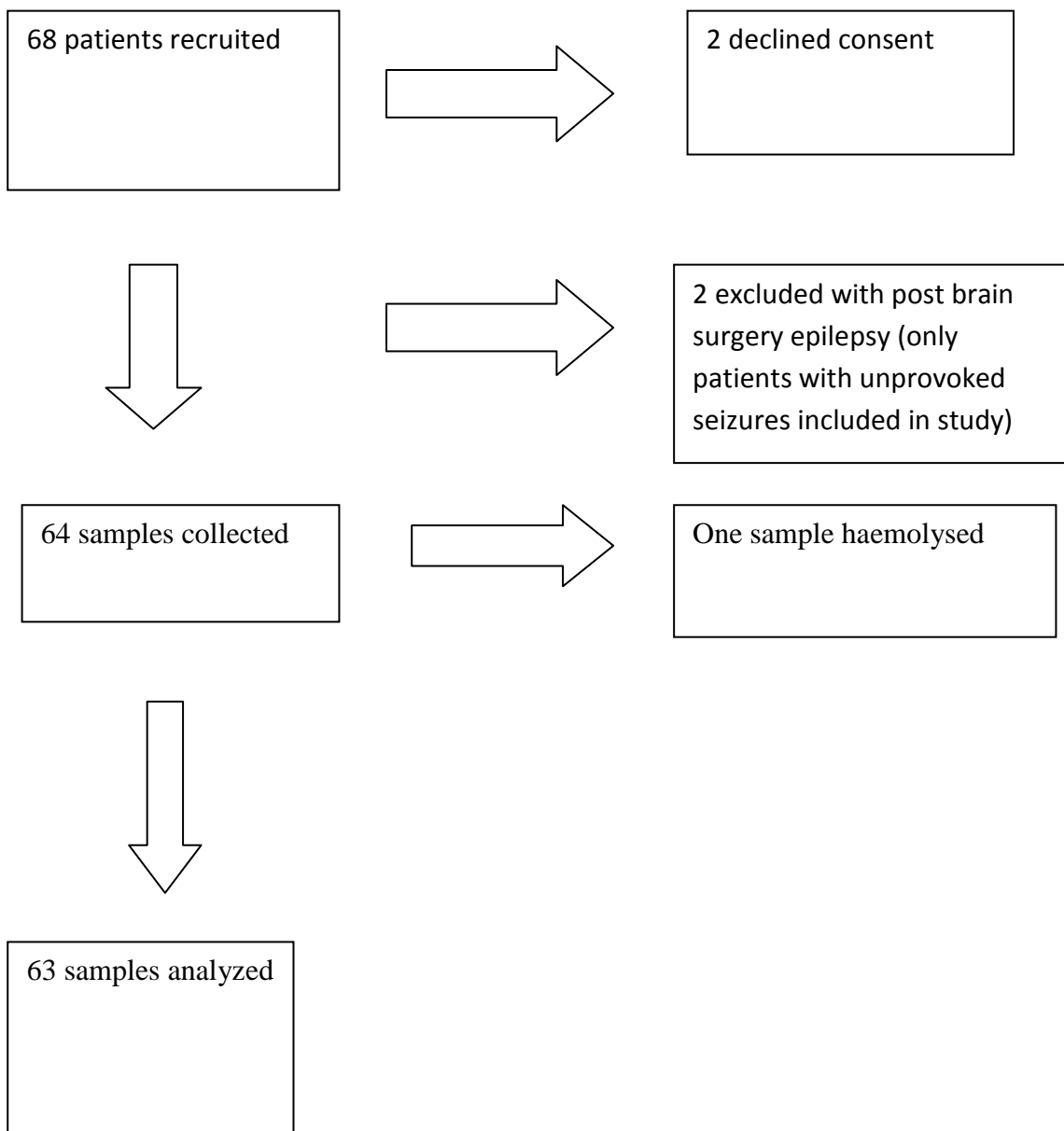


Table 1: Socio-Demographic Data Characteristics of Cases and Comparative Groups

Variable	Cases N(%)	Comparison group N(%)	P value
Mean age in years(SD)	29.7(10.1)	29.2(9.6)	0.778
Education level			
No education	2(2.3)	0	0.954
Primary	15(23.8)	17(26.9)	
Secondary	35(55.6)	36(57.2)	
Post-secondary	11(17.5)	10(15.9)	
Employment status			
Unemployed			0.436
Self employed	28(44.4)	26(41.3)	
Employed	11(17.5)	17(27.0)	
	24(38.1)	20(31.7)	
Marital status			
Single	39(61.9)	28(44.5)	0.061
married	24(38.1)	35(55.5)	

AGE

The mean age of the study participants was 29.7±10.1 years. This closely compared with the comparative group whose mean age was 29.2±9.6 years. There was no statically significance difference in the ages of the two group(P=0.7780)(Table 1).

The study participants age was normally distributed as shown in table 2.In the comparative group majority of them were aged between 21-30 years(44.4%).The age distribution for the comparative group was also normal.(Table 2)

EDUCATION

Majority of patients in the study group had post primary education with 73.1% having at least secondary education. This was comparable to the comparative group which had 73% of the participants having attained secondary level of education and above. No statistically significant difference was noted in education levels of the two groups ($p=0.954$). (Table 1)

EMPLOYMENT

44.4% of the patients were not engaged in any meaningful employment with 38.1% in formal employment. In the comparative group 31.7% were in formal employment with 41.3% not in any form of employment. There was no statistically significant difference in the employment status of the two group ($p=0.436$). (Table 1)

MARITAL STATUS

Majority of the patient in the study group were single (61.9%) .In the comparative group 55.5% were married, however the difference in the marital status between the two groups was not statistically significant ($P=0.061$). (Table 1)

Table 2: Age distribution of both cases and comparative group

variable	Cases N(%)	Comparative group N(%)	P value
Age group			
<=20	16(25.4)	13(20.6)	0.520
21-30	20(31.7)	28(44.4)	
31-40	16(25.4)	12(19.0)	
41-50	11(17.5)	10(15.9)	

Majority of the cases were aged between 21-40 years (57.1%). Similar age distribution was also found in the comparative group with those in the 21-40 years age group accounting for 63.4%.

Figure 3: Age distribution of cases

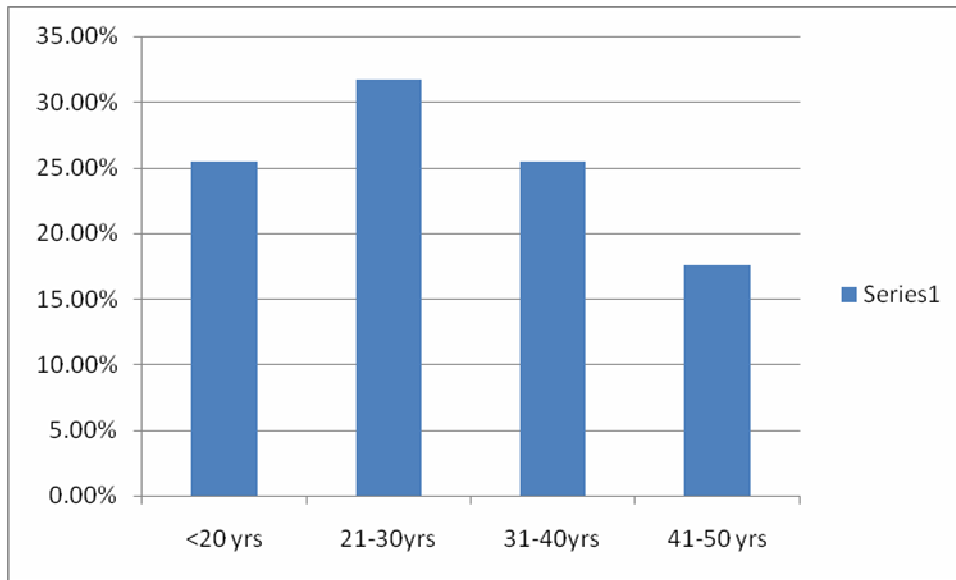


Figure 4: Age distribution of comparative group

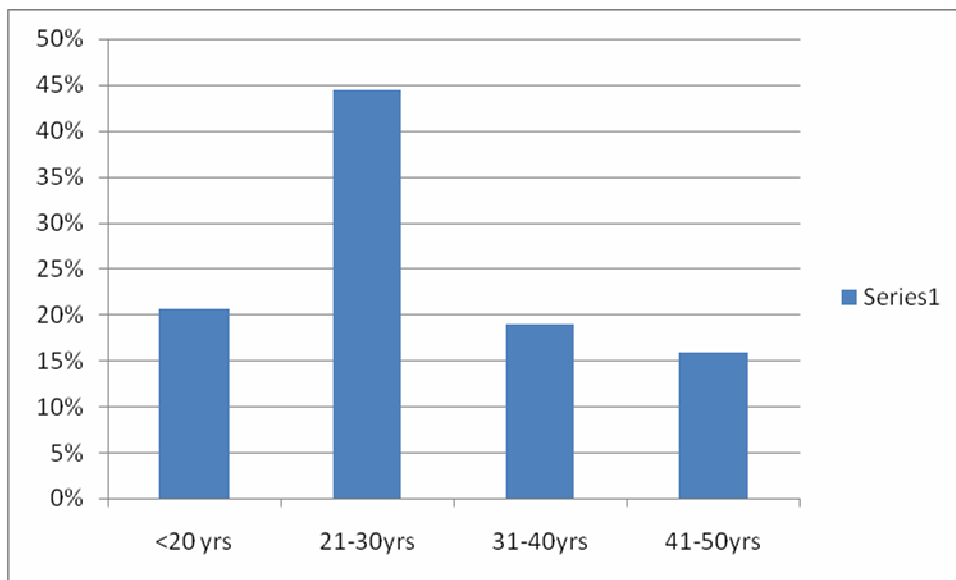


Table 3: Type of Epilepsy

VARIABLE	FREQUENCY(%) (n=63)
Type of epilepsy	
Absence seizure	2(3.2)
Complex partial seizure	18(28.6)
Generalized tonic clonic- seizures	43(68.2)

Most patients had generalized tonic- clonic seizures accounting for 68.2% of all the cases with a minority having absence seizures(3.2%).(Table 3)

Table 4: Drug type

VARIABLE	FREQUENCY(%) (n=63)
Drug type.	
Carbamazepine	50(79.4)
Phenobarbitone	10(15.9)
Phenytoin	19(30.2)
Valproate	13(20.6)
Rivotril	6(9.5)

Carbamazepine was the most common anti –epileptic drug prescribed either as monotherapy or in combination. 79.4% were on carbamazepine with rivotril (9.5%) and phenobarbitone(15.9%) as the least prescribed drugs .(Table 4)

Table 5: Number of drug combinations

VARIABLE	FREQUENCY(%) (n=63)
Number of drugs	
Monotherapy	34(54%)
Dual therapy	24(38.1%)
Triple therapy	5(7.9%)

Majority of patients were on monotherapy (54%) with 7.9% of patients on three drugs .The commonly used drug combination was carbamazepine/phenytoin combination. All the five ((5) patients who were on triple therapy were on CBZ/PHT/VAL combination.(Table 5)

Table 6: Enzyme inducers versus non –enzyme Inducers

VARIABLE	FREQUENCY(%) (n=63)
EIAEDs	61(96.8)
Non -EIAEDs	2(3.2)

Majority of the patients (96.8%) of patients were on at least an EIAED either as monotherapy or combination therapy (Table 6)

Table 7: Duration of therapy

Median (IQR)	8(3.0-12.0)
Range	0.5-35

The median duration of therapy was 8 years with a range of 0.5-35 years.(Table 7)

Table 8: Comparison of Testosterone, Sex hormone Binding Globulin and Free Androgen Index between cases and comparative group.

Variable	Cases(N=63) Mean (SD)	Comparative group(n=63)	P value
Testosterone (nmol/l)	22.1(8.2)	15.3(8.2)	<0.001
SHBG (nmol/l)	62.9(27.0)	44.6(26.7)	<0.001
Free Androgen Index	38.4(14.4)	38.9(18.7)	0.873

The mean total testosterone levels were higher in the study group compared with the comparative group and this was found to be statistically significant(22.1 ±8.2 mmol/l versus 15.3 ±8.2mmo/l ,p=<0.001).

SHBG levels were higher in the study group compared to the comparative group and this was statically significant(62.9±27.0 mmo/l vervus 44.6±26.7 mmol/l,p=<0.001).

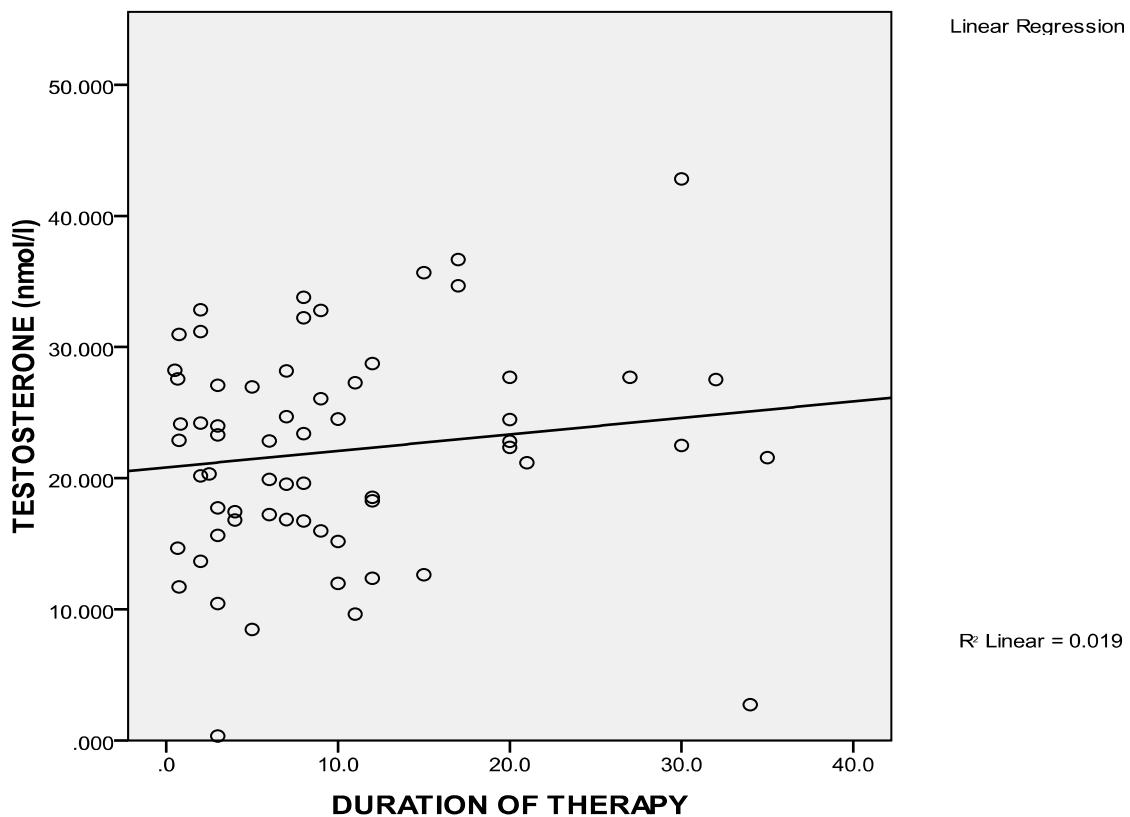
However the free androgen index was comparable in the two groups (38.4±14.4 versus 38.9±18.7,p=0.873) with no statically significant difference.(Table 8).

Table 9: Correlation between duration of therapy of anti-epileptic drugs, testosterone and Sex Hormone Binding Globulin levels

Variable	Pearson correlation coefficient(r)	Beta(β) coefficient	95% confidence interval of β	P value
Testosterone(nmol/l)	0.138	0.126	-0.105,0.357	0.281
SHBG (nmol/l)	0.195	0.586	-0.168,1.341	0.125

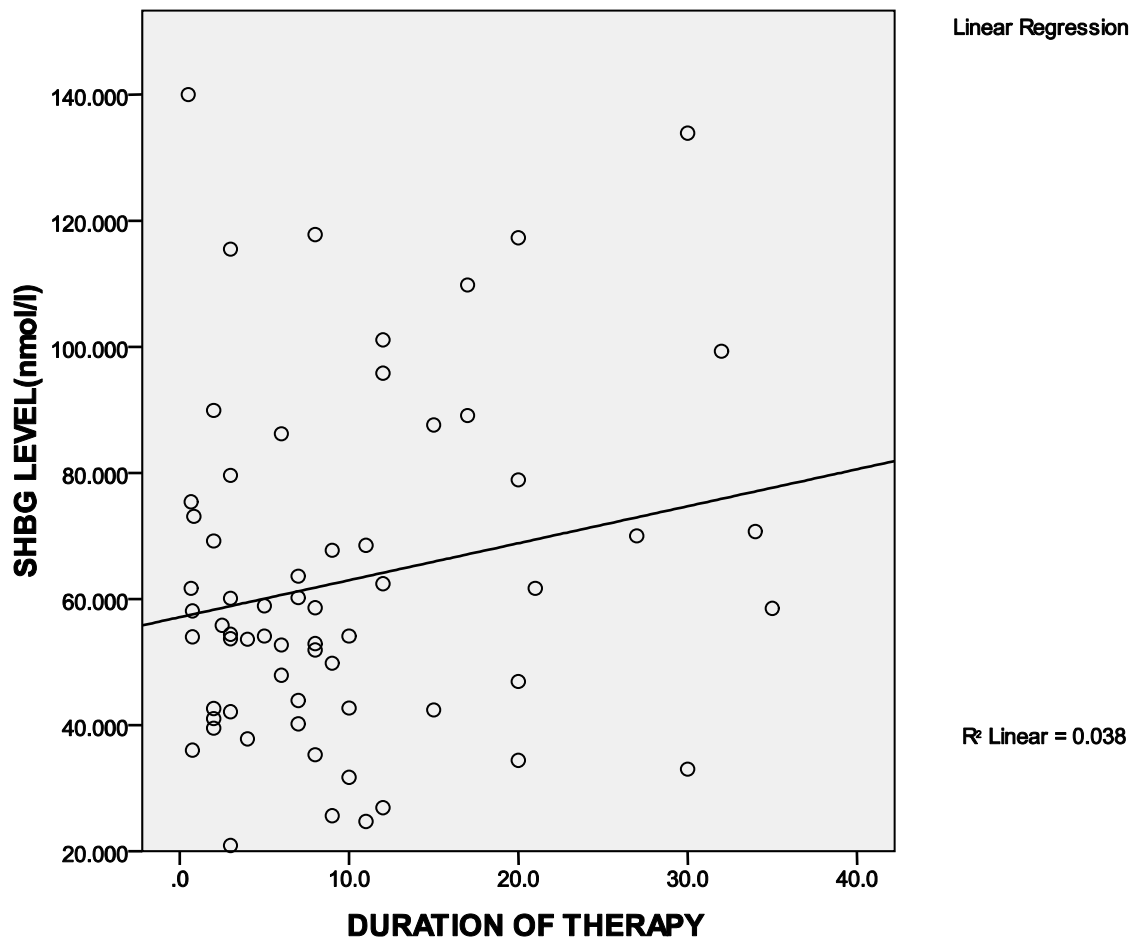
No correlation was found between levels of both testosterone and SHBG and the duration of therapy of AEDs.(Table 9).

Figure 5: Linear regression curve on association between total testosterone and duration of therapy



No correlation was found between duration of therapy with Anti-epileptic drugs and levels of total testosterone. (Figure 5)

Figure 6: Linear regression curve on association between sex hormone binding globulin and duration of therapy



No correlation was found between duration of therapy with Anti-epileptic drugs and levels of sex hormone binding globulin. (Figure 6)

Table 10: Comparison of Testosterone Sex Hormone Binding Globulin and Free Androgen Index between groups based on number of drugs

Variable	monotherapy	Dual therapy	Triple therapy	P value
Testosterone(nmol/l)	22.4(9.0)	21.2(7.7)	24.4(3.7)	0.693
SHBG level(nmol/l)	63.9(33.0)	57.9(12.5)	80.0(30.1)	0.239
Free Androgen Index	39.7(15.3)	37.4(13.1)	34.0(16.8)	0.659

The levels of testosterone were comparable in all patients whether receiving monotherapy or multiple AEDs.

SHBG levels were highest in the group receiving triple therapy (80.0±30.1mmol/l) and lowest in the dual therapy group(57.9±12.5mmol/l),however no statically significant difference was note among the three groups.

Free androgen index was comparable in the three groups.(Table 10).

Table 11: Comparison of Testosterone, Sex Hormone Binding Globulin, Free Androgen index between patients on Enzyme Inducing Anti-epileptic drugs non-Enzyme inducing Anti-epileptic drugs.

Variable	EIAEDS	NON-EIAEDS	P VALUE
Testosterone(nmol/l)	22.3(8.2)	16.4(8.4)	0.324
SHBG levels(nmol/l)	64.1(26.6)	27.7(9.5)	0.060
Free Androgen Index	37.7(14.2)	57.5(10.6)	0.057

Testosterone levels were higher in the group receiving enzyme inducing anti-epileptic drugs compared to the non-enzyme inducing drugs (22.3±8.2 nmol/l versus 16.4±8.4nmol/l ,p=0.324),however this did not achieve statistical significance. Similarly SHBG levels were higher in the EIAEDs group compared to the Non-EIAED(64.1±26.6nmol/l versus 27.7±9.5 nmol/l,p=0.060).The free Androgen index was higher in the non-EIAEDs group compared to the EIAEDs group(57.5±10.6nmol/l versus 37.7± 14.2nmol/l,p=0.057),the difference was however not statically significant. It's important to point out that only two patients out of the sixty three were on Non-EIAEDs, both were on sodium valproate as a single agent. (Table 11).

8.0 DISCUSSION

This study found elevated levels of testosterone in the study cases compared to the comparative group. (22.1 ± 8.2 nmol/l versus 15.3 ± 8.2 nmol/l, $p < 0.001$). This increase is thought to be due to decrease in biologically active testosterone as a result of increase in sex hormone binding globulin. The decrease in the level of SHBG leads to stimulation of the hypothalamic-pituitary-gonadal axis to produce more testosterone. The decrease in the levels of biologically active testosterone also results in reduced negative feedback input on the hypothalamus and pituitary resulting into production of GnRH, LH which in turn stimulate the testes to produce more testosterone. Similar findings of either normal levels or increased levels of testosterone have been demonstrated in other studies. Barragy et al [19], measured TT and SHBG levels in twenty nine (29) patients. TT levels were higher in those receiving AEDs than in normal control group (30 ± 17.1 nmol/l versus 16 ± 3.7 nmol/l, $p = 0.02$). Murialdo et al [22] in a study involving 37 adult male patients with epilepsy receiving AED monotherapy and were seizure free and had normal EEG findings, found no changes in levels of total testosterone, the study demonstrated reduced levels of free testosterone, dihydrotestosterone in the epileptic cases compared to the normal controls. Those found to have reduced levels of free testosterone had higher levels of impotence and sexual desire. Increased levels of SHBG were also demonstrated in the epileptic group compared to the normal controls. Findings of increased mean levels of testosterone were also demonstrated by Duncan et al [23] in a study one hundred and eighteen (118) men with epilepsy on anti-epileptic drugs, thirty two (32) with epilepsy not on treatment and thirty four (34) normal controls. Significantly elevated mean levels of Total testosterone and Sex hormone binding globulin were found in the treatment group compared to both the epileptic group not on treatment and normal healthy controls. The increase in total testosterone is not thought to have an influence on sexual functioning; it's the free testosterone which is thought to have effect on sexual function and fertility. Free testosterone was not measured in our study but Free Androgen Index was determined which can be used as a surrogate for free testosterone.

Some of the factors that would have affected the levels of testosterone and sex hormone binding globulins in our study include compliance to AEDs medication, measurement of the AEDs drug

levels in serum and correlation of the same with levels of both testosterone and sex hormone binding globulin. This was done in most other studies.

Correlation of sexual functioning, fertility and impotence and hormone levels was also not done in this study. This could be an important aspect within clinical significance in the care of epileptic patients with a decrease in sexual functioning being a consistent finding in all other studies that explored this aspect. Improvement in sexual functioning and fertility has also been demonstrated in patients with epilepsy on Anti-epileptic drugs with hypo sexuality and receive androgen supplementation.

Our study found increased levels of Sex Hormone Binding Globulin level in the Men with Epilepsy on Anti-epileptic drugs compared to the comparative group. (62.9 ± 27.0 nmol/l versus 44.6 ± 26.7 nmol/l, $p < 0.001$). The increase is as a result of increased hepatic synthesis of Sex Hormone Binding Globulin induced by the Anti-epileptic drugs. This finding is consistent with the findings of other studies that have demonstrated increase in SHBG in patients taking Anti-epileptic drugs. Barragry et al [19] demonstrated increase in SHBG levels in MWE on Anti-epileptic drugs compared to normal controls (7.3 ± 1.4 nmol/l versus 5.76 ± 0.82 nmol/l, $p < 0.001$). Talbot et al [17] also demonstrated increased levels of SHBG in sixty patients on various Anti-epileptic drugs compared to controls. The increase in SHBG binds testosterone causing decrease in free testosterone which is the biologically active portion of testosterone. This is what is thought to be the cause of decrease in sexual functioning and fertility in Men with Epilepsy on Anti-epileptic drugs. The increase in SHBG in excess of the compensatory increase in total testosterone is thought to be the cause in reduced Free Androgen Index in patients on Anti-epileptic drugs.

Free Androgen index was found to be comparable between the cases and the comparative group (38.4 ± 14.4 versus 38.9 ± 18.9 , $p = 0.873$). This was an inconsistent finding with most of other studies. Isojarvi et al [16], Barragry et al [19] had demonstrated statistically significant decrease in the Free androgen index in the epileptic groups compared to controls. Some of the factors that might have contributed to this finding in our study were poor compliance to medication, reduced drug levels in blood. The other studies were able to determine compliance and Anti-epileptic drug levels and correlated the two factors to Free Androgen Index, this was not done in this study. The cross sectional design of our study may also have contributed to this inconsistent

finding. Most of the other studies prospectively determined the Free Androgen Index serially over a period of time and were able to demonstrate significant changes in Free Androgen Index.

Our study did not find any difference in Free Androgen Index between the study group and the comparative group. Free Androgen index, a calculated value can be use as surrogate marker for measured free testosterone. Our study did not measure anti-epileptic drug levels or determine compliance on anti-epileptic drugs and this may have affected the levels of both SHBG and total testosterone. This would affect the calculated FAI. This finding on Free Androgen Index was an inconsistent finding from other studies that have shown reduced Free Androgen Index in epileptic patients on Anti-epileptic drugs.

Duration of therapy with AEDs was not found to have any correlation with levels of both Total testosterone and SHBG. A Pearson correlation coefficient(r) of(0.138, $p=0.28$) was found for testosterone levels and duration of therapy. A value of(0.195, $p=0.125$) was found for SHBG. This was different from the findings of Isojarvi et al [15] 1995 who had followed up twenty one(21) patients on PHT and CBZ for five years. Serum TT did not change during period of treatment, however the study found significant increase in SHBG levels over the five year period. A positive correlation was found between serum SHBG and duration of therapy($r=0.605$, $p<0.05$).

This study found higher levels of both Total Testosterone(22.3 ± 8.2 nmol/l versus 16.4 ± 8.4 nmol/l, $p=0.324$) in the group receiving Enzyme inducing Anti-epileptic drugs compared to those on non-enzyme inducer Anti-epileptics. Similarly higher levels of SHBG were found in the Enzyme inducing group compared to the non-enzyme inducing group (64.1 ± 26.6 nmol/l versus 27.7 ± 9.5 nmo/l, $p=0.060$). Free androgen Index was also higher in those receiving non- enzyme inducing drugs compared to those on enzyme inducers (57.5 ± 10.6 versus 37.7 ± 14.2 , $p=0.057$). The study demonstrated tendency to increase in both Total Testosterone and SHBG levels in the group on Enzyme inducers compared to non-enzyme inducers, however the differences did not achieve statistical significance.

However in this study only two patients(2.3%) were one Non Enzyme inducing Anti-epileptic drugs only Majority of the patients(96.8%) were on Enzyme inducing Anti-epileptic drugs either

as monotherapy or in combination. This finding is consistent with findings of Herzog et al [18] who compared levels of Biologically active testosterone and Sex Hormone Binding Globulin levels in 36 patients receiving Enzyme Inducing Anti-epileptic drugs and eighteen(18) on lamotrigine(Non-EIAED) and nine(9) normal controls. Biologically Active Testosterone levels were significantly lower in the Enzyme Inducing Anti-epileptic drugs group than in the lamotrigine and normal control groups.

Free Androgen Index was higher in the non-enzyme inducing group compared to the enzyme inducing group (57.5 ± 10.6 versus 37.7 ± 14.2 , $p=0.057$), this was however not statistically significant. This could be due to the small numbers of patients on non enzyme inducing drugs in our study. It's important to point out that only two patients were on a non enzyme inducing drug, both were on valproate as a single drug. Carnile et al (1997) [21] demonstrated that non enzyme inducing AEDs offered an advantage in the area of reproductive endocrine function in that they don't enhance metabolism of testosterone. He studied thirty seven(37) patients with epilepsy on lamotrigine alone. Total testosterone, Sex Hormone Binding Globulin and Free androgen index levels were found not to be increased compared to levels in normal healthy controls.

9.0 CONCLUSIONS

This study showed that men with epilepsy on Anti-epileptic drugs had higher concentrations of both Total Testosterone and Sex Hormone Binding Globulin than normal healthy aged matched men. However Free Androgen Index was not reduced in the male patients compared to the comparative group. There was no correlation between duration of therapy with AEDS and the levels of total testosterone and Sex Hormone Binding Globulin. The study did not find any difference in the levels of testosterone and Sex Hormone Binding Globulin levels in patients receiving Enzyme inducing Anti-epileptics and those on non enzyme inducers.

10.0 RECOMMENDATIONS

Further studies correlating levels of testosterone, sex hormone binding globulins and free androgen index with sexual functioning.

A prospective study with serial measurement of Total testosterone, Sex Hormone binding Globulin and Free Androgen Index in patients on Anti-epileptic drugs to be able to determine the long term effects of these drug on patients sexuality.

Further studies involving large number of patients on non enzyme inducing anti-epileptics to be able to determine whether patients on non enzyme inducers have a better male hormone profile than those on enzyme inducing drugs.

11.0 STUDY LIMITATIONS

Due to financial constraint I was not be able to assay AEDs levels. The inability to perform thyroid function tests, renal function tests and liver function test due to financial constraints may have lead to inclusion into the study of patients/comparative subjects with clinically inapparent disease. Low number of patients on Non –enzyme inducing AEDs may affect ability of the study to make comparisons with those on Enzyme inducing anti-epileptic drugs.

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APPENDIX 1: A COMPARATIVE STUDY OF TESTOSTERONE,SEX HORMONE BINDING GLOBULIN AND FREE ANDROGEN INDEX LEVELS IN MEN WITH EPILEPSY AT KENYATTA NATIONAL HOSPITAL NEUROLOGY CLINIC.

Purpose of the study.

I Dr. Musyoki Francis an undertaking this study on the effects of AEDs on male reproductive hormones in Kenyatta National Hospital .AEDS are known to cause low levels of male hormones which may affect their reproductive function.

Procedures

You are being asked to participate in this study that will take about 30 minutes. If you agree to participate I will ask you to sign a consent form. There will be questions that I will ask you in confidence and answers noted down. I will also do a physical exam to look for signs of secondary sexual characteristics, renal, thyroid or liver disease.

There after my assistant /or I will collect from you a blood sample of about 5mls that will be taken to the laboratory for measurement of Total testosterone and SHBG levels and calculation of FAI.

The test results will be revealed to you (results in file) soonest possible for your continued care. Tests results shall remain confidential.

Risks to you as a participant

There will be some discomfort from the needle prick at the site of blood sample removal (usually from the cubital area or any other appropriate site).

Rarely swelling or bleeding may occur from the puncture site but will make sure bleeding has stopped before I leave. In the event that bleeding appears kindly contact me or any nearest health worker for assistance.

Benefits

You will not be charged for any of the laboratory tests. The findings of the physical examination and laboratory tests will form part of your usual care. Proper advice on the choice of AEDs will be given to you based on the laboratory findings. Copies of the test results shall be availed to the patient (in the patient file).

This is the first time the study is being done in Kenya in Epileptic patients and the findings may go a long way in helping both the patient and health worker in choosing type of AEDs.

Right to refuse

Your participation in this research is voluntary. You are free to withdraw from the study any time and you shall not be discriminated upon. You are free to ask any questions and have right to satisfactory answers before you sign the consent form.

Permission to carry out this study has been sought and granted by KNH/UON ERC. This committee is charged with the responsibility of ensuring that all ethical considerations have been met. The committee also ensures that the interests of the participants are taken care of and no undue harm is done to the participants of this study.

Any questions/clarifications on this study may be sought from ,

SECRETARY,KNH/UON-ERC

[TEL:020-2726300](tel:020-2726300) ext 44102.

If you agree to participate in this study may you kindly sign on the consent form.

Thank you.

APPENDIX 2: CONSENT FORM

I.....

..... consent to participate in the study A COMPARATIVE STUDY OF TESTOSTERONE ,SEX HORMONE BINDING GLOBULIN AND FREE ANDROGEN INDEX LEVELS IN MEN WITH EPILEPSY AT KENYATTA NATIONAL HOSPITAL NEUROLOGY CLINIC. I do this with the knowledge of the purpose of the study and the procedures have been explained to me clearly by DR.MUSYOKI FRANCIS or his assistant. I am aware that I can withdraw from this study without losing any benefits and quality of care of my medical condition.

Signature of patient

Date

.....

Signature of witness.....

Date

.....

If you have any questions during course of the study , you may contact the following.

DR. MUSYOKI FRANCIS

Mobile number. 0713386144.

OR

The Chairman of the Ethical and review Committee

Kenyatta National Hospital

Tel 020-2726300/ 0722-829500/0733-606400 Ext 44102.

APPENDIX 3: DATA COLLECTION QUESTIONNAIRE

Age: _____

Hospital number _____

Date and time of interview _____

Study serial number (Code No.) _____

Contact and phone number where possible _____

Marital Status: Married Single

Education level:	No education	<input type="checkbox"/>	
	Primary	<input type="checkbox"/>	education
	Secondary	<input type="checkbox"/>	education
	Past	<input type="checkbox"/>	Secondary

Employment:	Employed	<input type="checkbox"/>	
	Self	<input type="checkbox"/>	employment
	Unemployed	<input type="checkbox"/>	

Seizure type
.....

DRUGS

Name	Dosage	Duration of Therapy

Testosterone Levels: _____nmol/litre

SHBG Levels: _____nmol/litre

Free androgen Index (Testosterone*100/SHBG)

APPENDIX 4: PHOTOGRAPH OF ARCHITECT MACHINE USED FOR DETERMINATION OF SEX TOTAL TESTOSTERONE AND SEX HORMONE BINDING GLOBULIN LEVELS

