SERUM URIC ACID LEVELS IN PATIENTS WITH BENIGN PAROXYSMAL POSITIONAL VERTIGO (BPPV): A CASE-CONTROL STUDY AT KENYATTA NATIONAL HOSPITAL

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A dissertation submitted to the University of Nairobi in partial fulfilment of the award of the degree of Master of Medicine in Otorhinolaryngology-Head and Neck Surgery, University of Nairobi.

2023

STUDENT'S DECLARATION

I declare that this is my original work, and it has not been presented for the award of any degree in any research institution or university.

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DEPARTMENTAL APPROVAL

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ABBREVIATIONS

BPPV-Benign Paroxysmal Positional Vertigo

BTU-Blood Transfusion Unit

CRP- Canalith Repositioning Procedure

ENT- Ear, Nose, Throat

KNH-Kenyatta National Hospital

Mg/dl-Milligrams per deciliter

SUA-Serum Uric Acid

SCC-Semi-circular canal

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ABSTRACT

Background: Benign paroxysmal positional vertigo (BPPV) is a peripheral vestibular disorder that contribute to dizziness and falls among afflicted patients. BPPV negatively affects the quality of life as it interferes with the patient's ability to perform daily activities. Serum uric acid levels have been linked as a risk factor for BPPV however there is no conclusive evidence on this causative relationship.

Objective: To compare the serum uric acid levels in patients with BPPV and controls in Kenyatta National Hospital.

Study Design and setting: This was a case-control study at the Ear, Nose and Throat clinic and the blood transfusion unit in Kenyatta National Hospital

Study population: The study involved a total of 33 cases aged 18 years and above diagnosed with BPPV and 33 age and sex-matched controls without a history of Vertigo at KNH from July 2022 to February 2023

Methodology: Patients diagnosed with BPPV through history and examination via the Dix Hallpike maneuver for posterior and anterior canal BPPV and supine roll test for lateral canal BPPV were included in the study. Serum uric acid level was determined. The process was repeated for the age and sex-matched controls drawn from the blood transfusion unit.

Data Analysis: Data was analyzed using STATA version 17. Continuous data was summarized using median (IQR). Categorical variables were summarized using frequencies and percentages. Rank sum test was used to compare medians of continuous data between cases and controls. Multiple conditional logistic regression was used to determine the association between BPPV and Serum uric acid (SUA) levels. Adjusted odds ratio (aOR) and the corresponding 95% confidence interval and p-value were reported.

Results: Most BPPV patients were female (70%) aged 30-56 years. The median serum uric acid levels were decreased in patients with BPPV compared to controls (224.5 umol/l vs

257.7umol/L) although the difference was not significant(p=0.350). There was no significant association between SUA levels and BPPV at a 5% significance level (aOR=0.997; 95% CI: 0.989, 1.005). The most common diagnosis was the right posterior semicircular canal BPPV with a prevalence of 73%.

Conclusion: This study showed that BPPV had a female preponderance in the ratio of 2.3:1. There was no significant difference in serum uric acid levels between cases and controls.

CHAPTER ONE: BACKGROUND

1.1 Introduction

BPPV is a peripheral vestibular condition characterized by brief episodes of vertigo brought on by particular postures of the head(1). The head positions that mostly cause symptoms are rolling over in bed on the affected side, lying down, and head extension (2). The vertigo is usually severe, rotatory and lasting less than a minute.

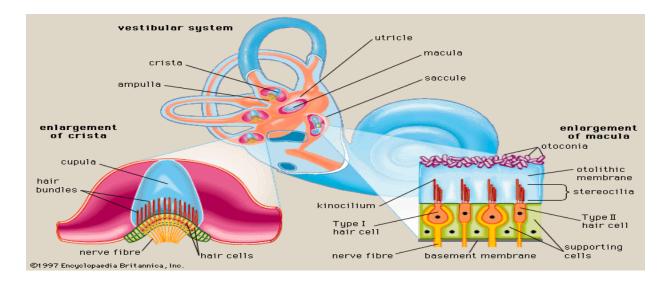
BPPV is the commonest cause of dizziness, accounting for 20-40% of peripheral vestibular system disorders(3). In the general adult population, it has a lifetime frequency of 2.4% and an estimated incidence of 107 per 100,000 per year (4). The most common cause of BPPV is idiopathic, followed by head and neck trauma. Other risk factors include vitamin D deficiency, Ear surgery, dental surgery, diabetes, hypertension and hyperuricemia (5).

Serum uric acid levels (SUA) have been linked as a causative factor for BPPV; however, the underlying pathophysiology remains unclear. Some existing theories include the fact that high uric acid levels cause an inflammatory response in the gelatinous matrix in which otoconia are lodged; hence can easily detach and deposit in one of the semicircular canals(6). High uric acid levels have also been linked in numerous studies to hypertension, cardiac issues, pre-eclampsia, renal failure, and cerebrovascular disease. (7,8,9)

Whether there is a causal connection between blood uric acid levels and BPPV is a matter of debate. Several studies done both globally and locally have yielded variable results, with some implicating high serum uric acid levels (10,11,12,13), some showing no relationship between serum uric acid and BPPV (14), and others showing low serum uric acid levels (15,16). Assessing this relationship could potentially uncover the outcome; since serum uric acid levels can be controlled pharmacologically, the effects could be reversed, which will greatly improve patient satisfaction with treatment outcomes.

1.2 Anatomy and physiology of the vestibular system

The vestibular system detects head movement and its position in space by sensing linear and angular acceleration (18). It consists of peripheral sensing organs, central processors and motor output. These components in conjunction with other sensory inputs including vision and proprioception coordinates movement between the eyes and head (19). Three simple reflexes describe the motor output of the central vestibular system: the vestibulo-ocular reflex (VOR), the vestibulospinal reflex (VSR) and the vestibulocollic reflex (VCR). The VOR enables clear vision by generating relevant eye movements while the head is in motion(20). By working on the muscles of the neck, the VCR stabilizes the head. The VSR maintains head and postural stability by generating compensatory body movement, preventing falls(21).





The labyrinth of membranous and bony tissue that makes up the peripheral vestibular system. The cochlea, vestibule, and semicircular canals make up the bone labyrinthThe membranous labyrinth has five sensory organs, including two otolith organs, the utricle, and three semicircular ducts. They contain endolymph which is rich in potassium and low in sodium. The semicircular canals are mechanoreceptors that sense angular rotation. The three semicircular canals, i.e., the horizontal, posterior and anterior canals, open into the utricle via five openings. The anterior and posterior semicircular canals share a common opening at the crus commune (23).

The semicircular canal (SCC) in each bony labyrinth is functionally paired and acts as complementary coplanar pairs. The right posterior and left anterior canals are oriented 45 degrees off the sagittal plane, and so is the left posterior and right anterior canals. The horizontal canal is structured 30 degrees off the axial plane. The plane of every pair of the semicircular canal is linked to specific extraocular muscles.

Each semicircular canal has an ampullated and a non-ampullated end. The ampullated end contains a sensory epithelium known as the crista ampullaris, which converts head movement signals into neurologic signals projected to the central vestibular system. Embedded in the crista ampullaris are polarized hair cells that project into a gelatinous cap called the cupula. Each hair cell consists of 70-100 stereocilia in rows that are initially short and increase in length to the kinocilium(24).

The cupula extends from the crista ampullaris to the canal's roof and sides, forming an impermeable barrier. Movement of endolymph causes deflection of the cupula that leads to either an inhibitory or excitatory reaction, depending on the particular semicircular canal and the direction of motion. Deflection of the cupula towards the kinocilium is excitatory, while deflection away from the kinocilium is inhibitory(25).

The otolith (utricle and saccule) contains a sensory epithelium known as the macula which has hair cells embedded in the otolith membrane. Embedded on the otolith membrane is calcium carbonate crystals called otoconia. The otoconia are made of calcium carbonate (CaCo3), combined with a protein matrix (about 40%) of the volume. The impulses produced by hair cells of the macula and the crista ampullaris are transmitted by the vestibular nerve which terminates at the vestibular nuclei.

1.3 Physiology of uric acid

Uric acid is produced from exogenous and endogenous purine metabolism in the body. Most of the uric acid produced in the body is from endogenous purine metabolism and about 1/3 is from dietary sources (26). In other mammals, uric acid is metabolized into allantoin by the hepatic enzyme uricase, which is a more soluble product. The level of solubility of uric acid in water is low, and in humans, the average serum uric acid concentration is close to the solubility limit. Monosodium urate (MSU) crystals occur and are deposited in joints and tissues when the serum uric acid level is more than 6.8 mg/dL. Hence uric acid levels in blood can rise if produced in excess and/or if its excretion from the body is slow.

1.3 Pathophysiology of BPPV

Two theories are attributed to the pathophysiology of BPPV. The cupulolithiasis hypothesis which states that otoconia from the utricle becomes adhered to the cupula in one of the semicircular canals usually the posterior canal causing increased density of attached otoconia to the cupula and produces excessive deflection during head movement in certain positions(27)⁻

The canalithiasis theory states that dislodged otoconia from the utricle that is free floating in the endolymphatic fluid in one of the semicircular canals, usually the posterior canal is moved into the most dependent position in the canal with head movement resulting in displacement of endolymph hence causing BPPV(28).

1.3.1. Pathophysiology of BPPV in relation to uric acid levels

The otoconia are connected and anchored to the gelatinous matrix by surface adhesion and are confined within a loose interconial filament matrix. It is proposed that increased uric acid levels in blood could lead to weakness in the structure of interconial matrix that embeds the otoconia on the supporting gelatinous matrix hence they can easily lodge off and deposit in the semicircular canals commonly the posterior semicircular canal.

Monosodium urate crystals develop when uric acid levels are elevated. There is suggestion that BPPV may be caused by a buildup of purine crystal deposits in the semicircular canals. The crystals trigger the movement of endolymph within the semicircular canals which the brain interprets as motion. (29)Experimental studies have shown that uric acid is a biologically active substance that increases inflammatory factors known to cause vascular destruction either by production of reactive oxygen species (ROS) and sub-endothelial dysfunction or by induced endothelin 1 secretion(30).ROS damage vasculature compromising blood supply to the inner ear. Reduced circulation of the utricle and saccule causes ischemia of the organ hence otoconia dislodge and are deposited in the semicircular canals.

There is evidence that if uric acid enters endolymph, it causes a reduction in PH which prevents the dissolution of otoconia. The low PH in endolymph destroys the balance between otolith dissolution and formation(31).

1.4 Clinical presentation of BPPV

These patients present with recurrent episodes of vertigo of less than a minute triggered by specific movements such as rolling over in bed, hyperextension of the neck and bending forward (32). The vertigo recurs over a period of weeks to months. The symptoms Wax and wane with time with spontaneous remissions but recur later. Some patients may complain of imbalance in between attacks (33). There are no auditory symptoms like tinnitus, hearing loss and aural fullness. The patients may also experience nausea and vomiting during the vertigo episodes.

1.5 Diagnosis of BPPV

The Dix Hall pike maneuver is used to diagnose anterior and posterior canal BPPV and the supine roll test to diagnose horizontal canal BPPV. The Dix Hall pike maneuver was first described by Barany in 1952 (5) The left posterior canal with the head turned left and the right posterior canal with the head oriented right are both tested individually. The Maneuver is done as the patient is seated on the examination couch; the head is turned 45 degrees to bring the canal being tested to a vertical position. The patient is then brought supine, neck extended 30 below the examination couch, and the eyes are observed for nystagmus.

The nystagmus onset has a latency of 1-5 seconds which is the time taken for the movement of otoconia to be initiated by gravity. The episodes last less than 1 minute which is the time taken for the otoconia to move to the most dependent position of the semicircular canal. The nystagmus is of vertical and torsional characteristics with the fast phase beating towards the

affected ear. The direction of nystagmus becomes opposite when the patient is brought in the upright position, and it wears out with repeated testing due to dispersion of otoconia in the semicircular canal.

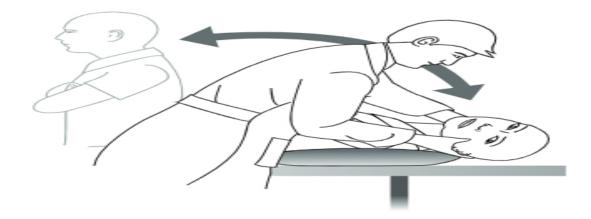


Figure 2: The dix hall pike maneuver(35)

Lateral canal BPPV is done by positioning the patient in the supine position, neck is flexed 30 degrees to orient the canal sagittally and then quickly turning the head laterally toward the side being tested. There is a horizontal nystagmus that is typically geotropic (fast component toward the earth) but can occasionally be apo geotropic (toward the sky).

1.6 Management of BPPV

Canal repositioning maneuver (CRP) based on the canalithiasis theory is the main stay mode of treatment for BPPV. These are repositioning maneuvers that, in cases of canalithiasis, use gravity to position the otoconia out of the affected semicircular canal and into the utricle. These maneuvers have been reported to have an efficacy of 85% resolution by first CRP(36).

In posterior canal BPPV repositioning maneuvers such as Epleys maneuver and the Semont maneuver are used(37). For the anterior canal BPPV the reverse Epleys and reverse Semont maneuver is commonly used. The Lampert/barbecue roll maneuver is used for lateral canal BPPV. Use of medication is highly discouraged by the American academy of otorhinolaryngology head and neck surgery because it interferes with habituation of the central vestibular system (38) .Medication should only be used in patients to reduce intensity of the vertigo and antiemetics to control nausea and vomiting.

Surgical options are mainly indicated for refractory BPPV. Options which include surgical occlusion of the affected canal with bony plugs rendering the canal nonfunctional. Argon Laser may be used to initiate ossification of the posterior canal. Resection of the posterior ampullary nerve can be done leading to deafferation of the posterior semicircular canal (39).

CHAPTER TWO: LITERATURE REVIEW

Over the past ten years, several research have been conducted to determine how blood uric acid and BPPV are related (10,11,12,13). The findings from these studies have been varied with some showing high levels of uric acid, low levels of uric acid, other inconclusive as to the relationship to BPPV.

A study by Celikbilek et al. in Turkey on the relationship between serum uric acid levels and BPPV discovered that BPPV patients had higher serum uric acid levels than healthy controls, who had a mean of 3.6mg/dl. The study comprised of 50 patients aged between 25 to 40 years with BPPV of unknown etiology and 40 age and sex matched controls. A follow up analysis of the SUA in BPPV patients one month after the attack revealed a significant decrement of SUA as compared to the ones obtained during the attack which further proves the hypothesis.(10). Regarding age and gender, the individuals with BPPV in his study showed no discernible differences.

Hyperuricemia has been shown to increase the risk of BPPV as seen in Mohammed et al study (11). The study aimed to demonstrate the effect of hyperuricemia on peripheral vestibular function. The study involved 40 patients aged between 40-55 years selected from a rheumatology clinic as compared to 40 age and sex matched healthy controls. Full history taking, vestibular evaluation and serum uric acid assay were undertaken by the principal researcher. Dix-Hall pike maneuver was positive in 9 subjects [22.5%] and they had higher mean SUA (8.06) levels compared to those without BPPV (7.74). The gender distribution in patients with BPPV in the study was in the ratio of males to females of 3:1.

Mohammed et al study agrees with Lin et al cohort study on the relationship between gout and BPPV in Taiwan (12).Lin et al identified a group of patients aged between 18 to 70 years with gout compared to four times age and sex matched controls in the general population and followed them up until they developed BPPV or till the end of the 3-year study period. The study found that 10.09 per 1000 person had BPPV during the follow up period. He concluded that patients affected with gout have a high chance of BPPV. The theory in this paper suggested that

the chemical constituents of the otoconia is due to buildup of purine crystals in the semicircular canals which are the causative factors for BPPV in gout patients.

A meta-analysis and systematic review of observational studies was done in China in February 2019 by Xing long yang et al(13). The aim was to gain an understanding of the potential association between SUA and risk of BPPV. A total of 12 studies conducted in China and outside China were analyzed in the meta-analysis. There was a strong likelihood for high SUA to be linked to BPPV among studies done in China but not in the studies done outside China. This shows that uric acid levels can be determined by the Geographical location of patients.

In East Africa, a study done in 2001 at a private neurological clinic by Adam to correlate serum uric acid with BPPV whereby he analyzed 90 patients who presented with vertigo (78 males and 12 females) and compared to healthy age and sex matched controls showed a strong correlation between high uric acid and BPPV(17). The study population comprised of 75 Africans,9 Asians and 6 Europeans. In this study the gender distribution was akin to Mohammed study with a male to female ratio of 4:1.

Whereas some studies have shown high SUA levels to be associated with BPPV, some authors had contrasting findings.

V Ziavra et al (14)study on the implication of serum uric acid in BPPV had SUA measurements taken in 20 subjects with BPPV (14 females and 6 males) aged between 23-79 years and the levels were compared with an age and sex matched group with various neurological conditions. Uric acid levels and BPPV were not statistically correlated, according to this investigation. The study population consisted of European females. This study was not able to elicit the relationship between BPPV and uric acid levels and this could be since the author had a small sample size.

A case control study by Ji Soo Kim et al recruited 168 patients (116 women,52 males) with confirmed diagnosis of BPPV and compared their serum uric acid levels with 194 age sex matched controls with no history of dizziness (15). The study found that the SUA levels were lower in cases than controls hence concluding that SUA is not a risk factor for developing idiopathic BPPV. Ji Soo Kim et al findings are like Togay et al retrospective study done to

determine predictive values of SUA in BPPV (16). Togay et al used patient files with BPPV and examined them and compared them with age and sex matched controls. With a mean value of 5.39 mg/dl in the control group compared to 4.45 mg/dl in the vertigo group, serum uric acid was found to be higher in the control group.

The type of SCC affected varied from study to study. Posterior SCC were predominantly affected in Celikbilek et al , Mohammed et al, Ziavra et al study having over 90% involvement(10,11,14) whereas Ji Soo Kim et al study showed 51% of the patients having posterior semicircular canal BPPV(15). The horizontal SCC involvement was demonstrated to be affected in celikbilek et al and Ji so Kim et al study however no patients with horizontal semicircular canal BPPV was seen in Mohamed and Ziavra et al study(10,11,14,15). The anterior SCC canal involvement was only seen in Ji so Kim et al study whereby he demonstrated 4.1% of patients.

2.1 Study Justification

With a prevalence of 2.4%, benign paroxysmal positional vertigo (BPPV) is the most prevalent cause of dizziness from the vestibular system (23). This disorder causes physical, functional, and even emotional disabilities that can affect patient's social lives and daily activities putting them at an increased risk of falls. The aim of this study is to seek the potential relationship between serum uric acid levels and BPPV. No studies have been carried out in KNH to determine this relationship. The study results will form substantive basis for whether serum uric acid should be routinely measured in patients with BPPV, and this may be used to guide treatment to reduce recurrence rates.

2.2 Study question

What is the serum uric acid level in patients with BPPV and how does the level differ from that of controls?

2.3 Study objectives

2.3.1 Broad objective

To compare the serum uric acid levels in patients with BPPV and controls in KNH.

2.3.2 Specific Objectives

- 1. To determine the demographics of patients with BPPV at KNH
- 2. To determine the serum uric acid levels in cases and controls in KNH
- 3. To determine the association between serum uric acid levels and BPPV at KNH

CHAPTER 3: RESEARCH METHODOLOGY

3.1 Study Design

This was a prospective case control study.

3.2. Study Setting

The study was conducted at the ENT outpatient clinic, blood transfusion unit (BTU) and biochemistry laboratory at Kenyatta National Hospital.

3.3 Study Duration

The study was carried out for a period of one year.

3.4 Study Population and sampling

3.4.1 Definition of cases

These were patients diagnosed with BPPV based on history and examination (Dix Hall pike and supine roll test)

3.4.2 Definition of controls

These comprised of age and sex matched controls without a history of vertigo who had been allowed to donate blood at the Kenyatta National Hospital Blood Transfusion Unit.

3.5 Inclusion Criteria

3.5.1 Inclusion criteria for cases

- a) Patients clinically diagnosed with BPPV aged 18 years and above in KNH.
- b) Patients who consented to the study.

3.5.2 Inclusion Criteria for controls

- a) Individuals allowed to donate blood at the Blood Transfusion Unit.
- b) Individual's age and sex matched with the study group.
- c) Individuals without history of vertigo.
- d) Individuals who consented to the study.

3.6 Exclusion Criteria

3.6.1 Exclusion criteria for cases

- a) History of head and neck trauma, patients with history of dental and ear surgery (major surgeries that involve drilling).
- b) Patients with diabetes and hypertension.
- c) Patients on drugs like thiazide diuretics and allopurinol.
- d) Patients with malignancy, chronic renal failure, gout, pregnancy, history of concomitant vestibular disorders.

3.6.2 Exclusion Criteria for controls

- a) Individuals clinically diagnosed with BPPV.
- b) History of head and neck trauma.
- c) Patients with history of dental and ear surgery.
- d) Patients with diabetes and hypertension.
- e) Patients on drugs like thiazide diuretics and allopurinol.
- f) Patients with malignancy, chronic renal failure, gout, pregnancy, history of concomitant vestibular disorders.

3.7 Sample size determination

The study by Yuan et al (13) was used to estimate the sample size based on the 2-sample normal approximation sample size formula:

Where:

n – Minimum sample size to be recruited in each group (i.e., the BPPV patients and individuals without BPPV)

 $z_{1-\alpha/2}$ – Standard normal distribution critical value for the desired \propto -level of significance. At $\approx 5\%$ level of significance, this value equals 1.96.

 $z_{1-\beta}$ – Standard normal distribution critical value for the desired power (power=1- β). At 80% power, i.e., β =0.20, this value equals 0.84.

 σ – Pooled (combined) standard deviation of uric acid level for both groups (=83 units based on yuan et al., year)

 μ_1 - Mean uric acid level in the healthy individuals i.e., the comparator group (=267 units based on yuan et al., year)

 μ_2 - Mean uric acid level in the BPPV patients i.e., the case group (=325 units based on yuan et al., year)

$$n=2(83)21.96+0.842(325-267)2\approx33$$
(325-267)2

Based on formula (i) and inserting the parameters given, the study recruited a minimum of 33 BPPV patients and 33 individuals without BPPV, giving a total of 66 participants.

3.8 Sampling technique

Cases and controls were recruited through successive convenient sampling up until the target sample size was achieved.

3.9 Study Procedure

3.9.1 Cases

The cases were selected from patients referred to the audiology department in the ENT clinic for vestibular assessment. The study was introduced to all the patients and the planned procedure was explained. Relevant history was taken to confirm BPPV. Full vestibular assessment test like the gait test, Romberg test, the Dix Hallpike manoeuvre and supine roll test was carried out.

The patient was then made to sit on the examination couch with Frenzel lenses on. The patient's head was turned 45 degrees to the right for the right posterior canal test, and 45 degrees to the left for the left posterior canal test. The patient was then brought supine and neck extended 30 degrees below the examination couch and the patients' eyes were examined for nystagmus. The horizontal semi-circular canal was then tested by laying the patient supine neck flexed 30 degrees to orient the canal sagittally and then turning quickly the patients head laterally towards the direction being examined.

BPPV-positive patients were required to complete an informed consent form that included a thorough explanation of the study's goals, its voluntary nature, its advantages, its confidentiality requirements, and its associated costs. Consequences of needle prick such as pain were explained by the principal investigator. On wearing clean gloves, the venipuncture site (cubital fossa) was cleaned with an alcohol swab. Four milliliters of venous blood was drawn using a disposable syringe as per KNH standard operating procedure for safe phlebotomy (KNH/LAB MED/SCM-003).

After blood was drawn, it was placed in a plain, red-topped vacutainer tube that was labeled with the patient's study number. Any extra blood was discarded as per KNH phlebotomy standard operating procedure. The sample was taken to the biochemistry laboratory at KNH, and serum uric acid levels was determined. It was centrifuged at 300 revolutions per minute for 3 minutes. The normal reference ranges between uric acid were 137-363mmol/l for males and 214-488mmol/l for females.

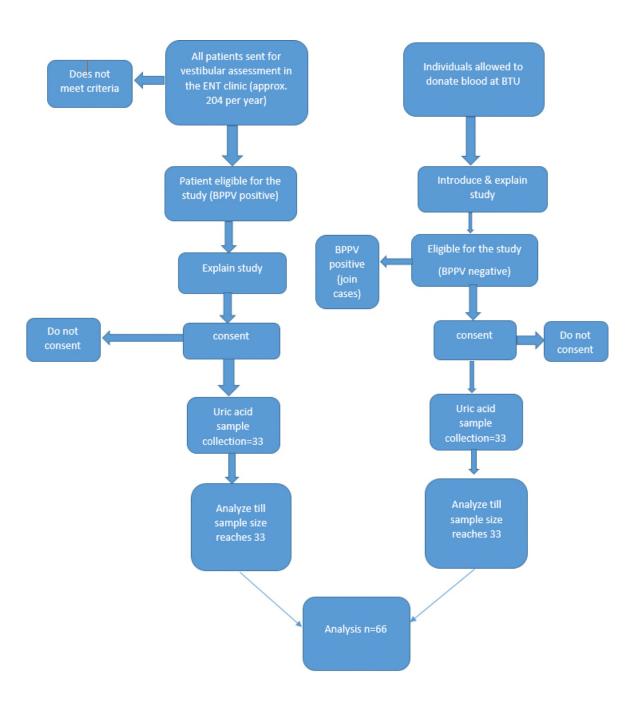
3.9.2 Controls

Controls were selected from individuals who had been allowed to donate blood at the BTU at Kenyatta National Hospital. The study was introduced, the planned procedure was explained, and they were asked to sign an informed consent. History was taken and a full vestibular examination like the gait test, Romberg test including the Dix Hallpike maneuver and log roll test was carried out to confirm clinical BPPV (**appendix 3**).

The subjects were asked to lie on the examination couch with Frenzel lenses on. The subject's head was turned 45 degrees to the right for the right posterior canal test, and 45 degrees to the left for the left posterior canal test. The subject was then brought supine and neck extended 30 degrees below the examination couch and the patients' eyes were observed for nystagmus. The lateral semicircular canal was tested by laying the subject supine neck flexed 30 degrees to orient the canal sagittally and then quickly turning the subject head laterally towards the side being tested. This was done before the blood donation process began.

On wearing clean gloves, the venipuncture site (cubital fossa) was cleaned with an alcohol swab. Four milliliters of venous blood was drawn as blood samples are being taken for screening as per KNH standard operating procedure for safe phlebotomy (KNH/LAB MED/SCM-003). Blood was drawn and placed in a plain, red-topped vacutainer tube that was labeled with the patient's study number. Any extra blood was discarded as per KNH phlebotomy standard operating procedure. The sample was then taken to the biochemistry laboratory at KNH and serum uric acid levels were determined.

3.9.3 Sampling procedure flow chart



3.10. Study Tools and equipment

Data collection sheet (**appendix 3**) Frenzel glasses with 10x magnifying lens. Examination couch Syringes and needles Alcohol swabs Vacutainer specimen collection tube-red top Bio soi analyzer machine

3.11 Data Management and analysis

Demographic data, history and physical exam findings and serum uric acid levels were recorded into a data collection sheet (**Appendix 3**). All forms and signed consents were stored safely. Soft copy details of the data were stored safely in a password protected computer. The data was accessed by the principal investigator and supervisors only.

The data was captured in Microsoft Access database. Thereafter it was exported to Stata version 15 for cleaning and analysis. Data cleaning was critical in identifying and correcting issues such as inconsistencies, duplicates, obvious outliers to ensure good data quality. Univariate analysis was done to explore the data. Continuous data such as age and serum uric acid level was summarized using means (SD)/median (IQR) depending on the distribution of the data. The distribution of this type of data was illustrated using a histogram. Categorical variables such as sex was summarized using frequencies and percentages. Illustration of categorical variables was done using bar charts and pie charts as appropriate.

Bivariate analysis was done to determine the crude association between the BPPV variable (coded 0 if participant do not have BPPV and 1 if he/she has BPPV) and the risk factor variables such as hyperuricemia. For continuous predictors such as uric acid level, student's t-test was used to compare medians/means (depending on the distribution of the continuous variable) between the two groups of participants, while for categorical predictors such as sex, Chi-squared test of association was used.

The relationship between uric acid level and BPPV was examined using multivariable analysis. To achieve this, multiple conditional logistic regression was used since the participants were matched (by age and sex). The model considers the matching. Measures of association such as odds ratio (OR) and the corresponding 95% confidence interval and p-value were reported. Logistic regression fits a binary outcome (presence or absence of BPPV) to a set of predictors using the logit link function. The predictors can be continuous or categorical.

3.12 Quality control

Pre-analytical errors

Blood samples collected were transported to the biochemistry laboratory by medical personnel.

Serum was separated and put in the Biolis Soi analyzer machine. This machine undergoes daily internal control and monthly external quality control. It is also calibrated every six months as per KNH standard operating manual.

Analytical errors

All tests were conducted according to the manufacturers' established standard operating procedures, which were interpreted based on the manufacturer's insert. Running samples of level one and level two controls for each set of assays ensured quality control. When a fresh bottle of reagent was used, controls were run; if a control fell outside of its acceptable range, the corresponding test results were deemed invalid, and samples were retested.

Post analytical errors

When transferring results from the designated laboratory numbers to the data entry form, care was taken to prevent post transcriptional mistakes.

3.13 Ethical considerations

Following permission from the KNH/UON Ethics and Research Committee and the KNH management, the study got under way. After the patient was made aware of the study's goal and procedures, their informed consent was obtained. But if they declined to take part, they received care as usual, without discrimination.

The information gathered was kept private and was solely utilized for study. By using patient codes that were similar to the patients' names, phone numbers, or other forms of identification, anonymity was preserved. Participants with abnormal laboratory results were properly referred for additional assessment and care. The controls who were found to be BPPV positive were referred to the ENT clinic for management and follow up.

The study results will be made available to the KNH, presented in medical conferences, and published in medical journals for the benefit of the medical profession and the lay public. The document will be available in electronic form on the UON website's e-repository.(http://erepository.uonbi.ac.ke).

3.14. Covid 19 regulation guidelines

To avoid transmission of Coronavirus 19, the principal researcher wore protective equipment which included masks, gown, gloves, face shield, shoe covers and head caps. Sanitization of the examination couch or chair where patient was being examined was done. During sample collection disposable tourniquet was used to minimize risk of transmission of the virus. This was in adherence to the KNH Covid 19 standard operating procedure.

CHAPTER 4: Results

Between July 18 and October 13, 2022, 33 patients and 33 controls were recruited from the blood transfusion unit and ear, nose, and throat department of the Kenyatta National Hospital. Out of the 33 controls in the study none had vertigo requiring to be converted to cases.

4.1. Age-group distribution by study group and sex

The age distribution was similar across study groups for both females and males (Figure 4). This depicts proper age-matched sample in both sexes. Female cases had a median age of 41 years (IQR: 28-56) while the female controls had 44 years (IQR: 31-55) and the median difference between study groups was not significant (p=0.974). Male cases had a median age of 49 years (IQR: 32-54) while male controls had 49 (IQR: 30-52) and the difference in the medians was not significant (p=0.909). In the study, males ranged in age from 17 years to 59 years, while females ranged in age from 16 years to 72 years. The females were more than the males in the ratio of 2.3:1.



Figure 3:Age-group distribution by study group and sex

4.2. Clinical profile: Uric acid levels in the study participants

At a glance, the distribution of SUA was right skewed across both study groups (Figure 5). Among the female cases, the SUA level ranged between 173.4 umol/L and 300.4 umol/L while in the males' cases, the level ranged between 201.2 umol/L and 434.4 umol/L.

In the control group, the SUA levels of females ranged between 153.2 umol/L and 410.2 umol/L while in males it ranged between 136.6 and 566.1 umol/L. In both study groups, the SUA level of most of the participants within the normal range. Among cases, 100% of the females and 90% of the males had normal SUA levels. In the control group, 95% of the females and 70% of the males had normal SUA levels.

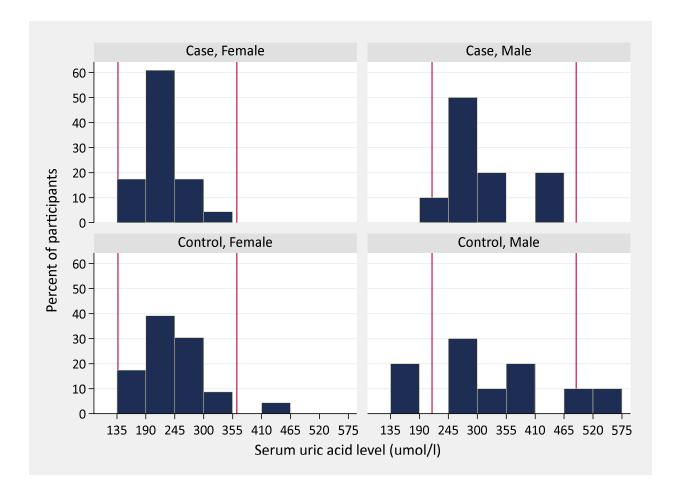
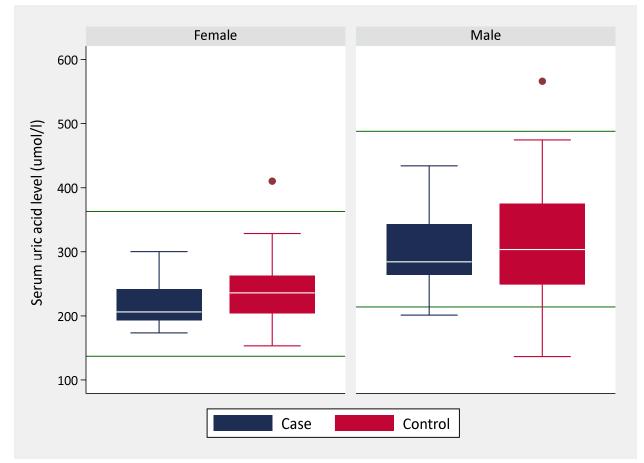


Figure 4:Distribution of SUA levels by study group and sex (red lines represent normal reference ranges)

4.3.Distribution of SUA levels by study group and sex

In both sexes, the distribution of SUA levels is as shown across study groups (Figure 6). Among the females, the cases had a median median SUA level of 206.1 umol/L (IQR: 193.1-241.5) while the controls had a median of 236.0 umol/L (IQR: 203.7-262.6) and the difference in these medians was not significant (p=0.100). In males, the cases had a median SUA level of 284.4 umol/L (IQR: 264.0-343.1) whereas the controls had a median of 303.5 umol/L (IQR: 248.8-375.2), the difference in the medians not being significant (p=0.912).

In both study groups, the males had significantly higher median SUA levels than females (Figure 2). In the case group, the median SUA of females was 206.1 umol/L while that of males was 284.4 umol/L (p<0.001). Among the controls, females had a median of 236.0 umol/L while males had 303.5 umol/L (p=0.042). Comparing the SUA levels in the same sex but different



study groups, the controls had higher (but not significant) median SUA in both females (controls vs cases, p=0.100) and males (controls vs cases, p=0.912).

Figure 5:Distribution of SUA levels by study group and sex

4.3 Diagnoses

The cases were diagnosed based on the vestibular test results. Results of the diagnoses were illustrated using bar charts with 95% confidence interval bars (Figure 5). The most common diagnosis was right posterior semicircular canal BPPV (prevalence=73%; 95% CI: 57% - 83%). About two thirds of the cases were diagnosed with left posterior semicircular canal BPPV (prevalence=64%; 95% CI: 47% - 80%). The other two diagnoses (right horizontal canal BPPV and left horizontal canal BPPV) had similar prevalence (15%; 95% CI: 3% - 28%). Approximately 2% of cases had multiple canal BPPV (Left posterior semicircular canal and right horizontal canal BPPV) None of the cases had bilateral canal BPPV.

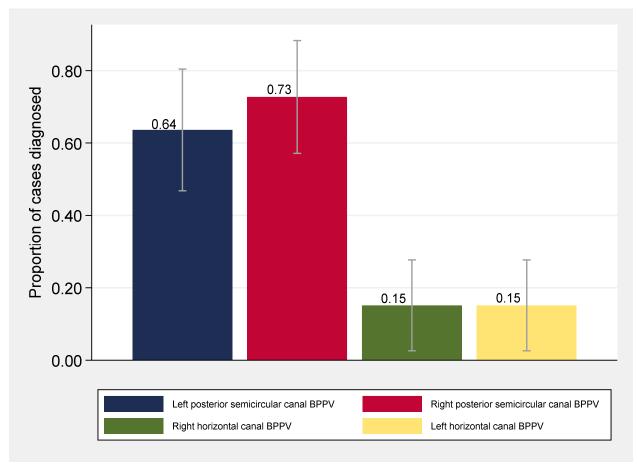


Figure 6: Final diagnosis of BPPV among cases (proportions and 95% confidence intervals)

4.4 Association between serum uric acid level, age and BPPV

The association between SUA and BPPV was determined using the conditional logistic regression since the participants were matched using age and sex. The dependent variable was the binary variable pertaining to patient group (case=1; control=0) while the main independent variable was the serum uric acid level in umol/L and the age.

There was no significant association between SUA levels and BPPV 5% significance level (OR=0.997; 95% CI: 0.989, 1.005). (Table 4).

Factors	Odds ratio	p-value	[95% Conf. interval]
Serum uric acid level (umol/L)	0.997	0.432	[0.989, 1.005]
Age (years)	1.025	0.720	[0.895, 1.174]

Table 3: Association between SUA, age and BPPV

CHAPTER FIVE: DISCUSSION, CONCLUSION & RECOMMENDATIONS

5.1: Discussion

There were 66 participants recruited into this study. The age range of participants was 45 - 60 years with a median age of 45 years among the cases and a median of 48 among controls. Similarly, Mohammed *et al* reported the most common age characteristics of patients with BPPV to be between 40-55 years (11). Celikbilek et al`s study also showed that the peak incidence of idiopathic BPPV occurred at 25-40 years of age with a median of 33.4 years (10). Our study contrasts with Ziavra et al, Ji Soo Kim et al and Yuan et al whose study population had a higher mean age of 53.25,55.2 and 63.4 years, respectively. (13,14,15). The study population in these studies consisted of an older age group as compared to our study.

In this study, there were more females with BPPV with a ratio of female to male at close to 2:1. This is like Ji Soo Kim et al's study that found that the number of female BPPV patients was greater than that of men (116vs 52) respectively (15). In addition, Ziavra et al also found that the incidence of BPPV in women was higher than that in men in the ratio of 2:1(67.31% vs 32.69%) respectively (16). In contrast, Adam et al's study found that most of the BPPV cases were African males (78 males and 19 females) (17). Similarly, Mohammed et al's study had more males with BPPV than females (7males vs 2 females) (11). Mohammed et al's s and lin et al's studies had different study population to our study as it recruited patients with gout which quite often tend to be males. (11,12).

Clinically, about 90.9% of patients reported history of vertigo with quick head movements,84.8 % had difficulty getting into and out of bed,81.8% had symptoms while bending over,69.7% while looking up,42.4% had nausea and 27.3% had vomiting. It was also shown from our study findings that the median duration since the last vertigo attack among the cases was one day. We found no other study that evaluated the clinical symptoms in patients with BPPV.

In this study, Dix-Hall pike test analysis revealed 73% of cases of BPPV were posterior canal. It was also noted that in most of these patients, the right ear was affected more at 73% followed by the left side at 64%. This finding suggesting a predominance of right ear BPPV was equally

reported by Celikbilek, Mohammed and Ziavra et al`s studies (10,11,14). The anterior SCC canal involvement was only seen in Ji so Kim et al study in 4.1% of patients. (15)

Uric Acid Levels and BPPV

According to the study's findings, there was no statistically difference between the cases (patients with BPPV) and the controls in terms of the likelihood that their serum uric acid levels would be high [OR. 0.997, 95 percent CI: 0.989, 1.005]. Even though the mean serum uric acid levels were slightly lower among the cases than the controls, this difference was notably not statistically significant (224.5 vs 253.7umol/l). As a result, although previous studies (10,11,12,13) suggested that having high serum uric acid levels could be a risk factor for developing BPPV, this study did not reach the same conclusion. The findings of this study are supported by studies such as a study by Ji Soo Kim et al which showed that the serum uric acid levels were decreased in patients with BPPV compared with controls (4.8 vs 5.3mg/dl, p=0.01). Similarly, Yuan et al found that BPPV group had lower uric acid as compared to controls 279.0umol/l vs 331.0umol/. However, there was no direct correlation between SUA level and BPPV P=0.713 (13).

Studies like Ziavra et alcase .'s control research in London, where he had 20 cases of BPPV and compared them with 20 age and sex matched controls, revealed similar serum uric levels in BPPV and control groups. Mean uric acid levels in patients with BPPV was 290.35umol/l (range from 150 to 475) and that of controls was 273.4umol/l normal values were from 134 to 470 umol/l. According to the study's findings, there was no statistically significant in the two groups' uric acid levels. (t-test, p=0.565) (14). Ziavra et al`s study like our study consisted of a small sample size.

Several other studies showed elevated uric acid levels in cases more than controls. Adam et al's case control study showed that the mean uric acid level was 442 +/- 16umol/l (CI 95%, P<0.001) for cases vs 291+/-17umol/l for the controls. Similarly, Celikbilek et al's study in a Caucasian population in Turkey showed that the average uric acid level in patients with BPPV was higher as compared to normal controls (4.85 mg / dl vs 3.6 mg / dl respectively<0.001). Adam`s study population like our study population consisted of Africans however the study had predominantly African males while our study had more females than males. Females are known to have high

estrogen levels which has been shown to be uricosuric (40). Zhu et al's study on relationship between BPPV and uric acid levels in the elderly (60 years) and above further supports this theory (16). The study findings reported high uric acid levels in cases than in controls(p<0.05). The cases were predominantly female. It has been shown at the age of 60 most women are postmenopausal and that estrogen levels which are uricosuric decline. Celikbilek et al's study is quite similar to our study in terms of the study design, but the findings are contrasting. The fact that the study was conducted on Caucasians in Turkey may also be responsible for the disparity in results. It is postulated that environmental or ethnic differences could have an influence on uric acid metabolism. Other factors could also influence serum uric acid levels such as nutritional and physical exercise habits.

Our study findings also differ from Mohammed et al's study whose findings demonstrated the dix-Hall pike maneuver to be positive in 9 subjects [22.5%] and they had higher mean SUA (8.06mg/dl) levels compared to those without BPPV (7.74mg/dl). The gender distribution in patients with BPPV in the study was 3:1 for males to females. Mohammed's work is comparable to Lin et alresearch .'s from Taiwan, which found a positive correlation between peripheral vertigo and gout. Our study differs from Lin et al and Mohammed et al's study due to that fact that the entry point into this study was patients with hyperuricemia and men are known to have a higher prevalence of gout as compared to women (40). Additionally, the increased incidence and prevalence of gout in males may be partially explained by differences in men's dietary and lifestyle habits..

A meta-analysis and systematic review of observational studies done by Xing long yang et al was aimed at understanding the potential association between SUA and risk of BPPV (1). A total of 12 studies conducted in China and outside China were analyzed in the meta-analysis. In studies conducted in China as opposed to those conducted outside China, significantly higher serum uric acid levels were seen in BPPV patients than in controls (OR = 0.78; 95 percent CI, 0.15-1.41; p = 0.015). This suggests that uric acid levels can be affected by the Geographical location of patients. The disparities and inconsistencies in earlier research from other continents, such as Asia and Europe, may in part be explained by differences in age, sex, racial background, metabolism, and lifestyles between nations.

5.2 Conclusion

This study showed that BPPV has a female preponderance in the ratio of 2.3:1.

The goal of this case-control study was to examine the relationship between blood uric acid and BPPV. Based on the findings, we can say that there is no conclusive link between serum uric acid levels and BPPV.

5.3 Recommendations

In our study we found no statistically significant difference in terms of uric acid levels between the cases and controls hence we do not recommend serum uric acid levels to be screened in patients with BPPV.

We recommend further studies with bigger sample size should be done to determine association of serum uric acid levels and BPPV.

5.4 Limitations

Thirty three participants made up our study's small sample size, which may make it harder to spot subtle or minute variations and limit the types of statistical analysis that can be run.

Table 1: Study time frame

The table below is a Gantt chart showing the time frame for my study.

Activity	Jan		Mar		Мау		Jul	Sep		Nov	Jan	Mar	M	ay	Jul	Sep	Nov	Jan	Mar	May
ALLIVILY		21		21		21	21	1	21	21	22	2 2	2	22	22	22	22	23	23	23
Proposal writing																				
Presentation																				
Ethics approval																				
Data collection																				
Data analysis																				
Presentation of																				
results																				

Table 2: Budget and Funding

Funding was sourced from Kenyatta National Hospital

Item	Cost
Stationery	20000
Statistician	35000
Uric acid test	Cases @300x33=9,900 Controls @300x33=9,900 Total= 19,800
Miscellaneous	20000
Total cost	94,800

REFERENCES

- 1. Furman JM, Cass SP. Benign paroxysmal positional vertigo. N Engl J Med. 1999 Nov 18;341(21):1590–1596.
- 2. Pearce JMS. Benign Paroxysmal Vertigo, and Bárány's Caloric Reactions. Eur Neurol. 2007;57(4):246–248.
- 3. Khan S, Chang R. Anatomy of the vestibular system: a review. NeuroRehabilitation. 2013;32(3):437–443.
- 4. Anatomy and Physiology of the Normal Vestibular System | Vestibular Rehabilitation | F.A. Davis PT Collection | McGraw-Hill Medical [Internet]. [cited 2021 Apr 29].
- 5. Glasscock ME, Gulya AJ. Glasscock-Shambaugh Surgery of the Ear. PMPH-USA; 2003. 910 p.
- 6. Lins U, Farina M, Kurc M et al. The Otoconia of the Guinea Pig Utricle: Internal Structure, Surface Exposure, and Interactions with the Filament Matrix. J Struct Biol. 2000 Jul 1;131(1):67–78.
- 7. Benn CL, Dua P, Gurrell R et al. Physiology of Hyperuricemia and Urate-Lowering Treatments. Front Med. 2018;5:160.
- 8. Serum uric acid as a harbinger of metabolic outcome in subjects with impaired glucose tolerance: the Finnish Diabetes Prevention Study PubMed [Internet]. [cited 2021 Jun 7].
- 9. Gagliardi ACM, Miname MH, Santos RD. Uric acid: A marker of increased cardiovascular risk. Atherosclerosis. 2009 Jan;202(1):11–17.
- 10. Celikbilek A, Gencer ZK, Saydam L et al. Serum uric acid levels correlate with benign paroxysmal positional vertigo. Eur J Neurol. 2014 Jan;21(1):79–85.
- 11. Al-Sobki MM, El-Zarea GA-A-R, Ahmed Mahmoud AM et al. Audio-Vestibular Findings in Patients with Hyperuricemia. Int J Med Arts. 2020 Oct 1;2(4):866–972.
- 12. Lin Y-T, Lin H-W, Huang Y-C et al. Association between gout and vertigo in a Taiwanese population. J Clin Neurosci. 2013 Jun;20(6):857–861.
- 13. Yang X, Yang B, Wu Met al. Association Between Serum Uric Acid Levels and Benign Paroxysmal Positional Vertigo: A Systematic Review and Meta-Analysis of Observational Studies. Front Neurol [Internet]. 2019 Feb 15 [cited 2021 Apr 7];10.
- 14. Ziavra NV, Bronstein AM. Is uric acid implicated in benign paroxysmal positional vertigo? J Neurol. 2004 Jan;251(1):115.

- 15. Jeong SH, Kim JS. The Effect of Serum Uric Acid in Generating Idiopathic Benign Paroxysmal Positional Vertigo. Res Vestib Sci. 9(1):27–31.
- 16. Evrin T, Katipoğlu B. Predictive Values of Serum Uric Acid, Mean Platelet Volume and Plateletcrit on Benign Paroxysmal Positional Vertigo. Eurasian J Emerg Med. 2019 Jun 20;18(2):95–98.
- 17. ADAM PROFAM. Adam AM: Benign positional vertigo and hyperuricaemia. East Afr Med J. 2005 Jul;82(7):376-8. Gitau, W., Ogallo L. A. and Mutemi, J. N.,; 2005.
- 18. Dickman JD, Huss D, Lowe M. Morphometry of otoconia in the utricle and saccule of developing Japanese quail. Hear Res. 2004 Feb;188(1–2):89–103.
- 19. Katsarkas A, Kirkham TH. Paroxysmal positional vertigo--a study of 255 cases. J Otolaryngol. 1978 Aug;7(4):320–330.
- Brodsky JR, Lipson S, Wilber J et al. Benign Paroxysmal Positional Vertigo (BPPV) in Children and Adolescents: Clinical Features and Response to Therapy in 110 Pediatric Patients. Otol Neurotol Off Publ Am Otol Soc Am Neurotol Soc Eur Acad Otol Neurotol. 2018 Mar;39(3):344–450.
- 21. Büki B, Ecker M, Jünger H et al. Vitamin D deficiency and benign paroxysmal positioning vertigo. Med Hypotheses. 2013 Feb;80(2):201–204.
- 22. Proprioception | biology | Britannica [Internet]. [cited 2021 Jun 4].
- 23. Bruintjes TD, van der Zaag-Loonen HJ, Eggelmeijer F et al. The prevalence of benign paroxysmal positional vertigo in patients with osteoporosis. Eur Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol Head Neck Surg. 2018 Dec;275(12):3083–3086.
- 24. Semicircular canal | anatomy [Internet]. Encyclopedia Britannica. [cited 2021 Jun 7].
- 25. Chu C-H, Liu C-J, Lin L-Y et al. Migraine is associated with an increased risk for benign paroxysmal positional vertigo: a nationwide population-based study. J Headache Pain. 2015 Jul 4;16(1):62.
- 26. Maiuolo J, Oppedisano F, Gratteri S et al. Regulation of uric acid metabolism and excretion. Int J Cardiol. 2016 Jun 15;213:8–14.
- 27. Schuknecht HF, Ruby RR. Cupulolithiasis. Adv Otorhinolaryngol. 1973;20:434–443.
- 28. Hornibrook J. Benign Paroxysmal Positional Vertigo (BPPV): History, Pathophysiology, Office Treatment and Future Directions. Int J Otolaryngol. 2011;2011:835671.
- 29. Chen DP, Wong CK, Tam LS et al. Activation of human fibroblast-like synoviocytes by uric acid crystals in rheumatoid arthritis. Cell Mol Immunol. 2011 Nov;8(6):469–478.

- 30. Chao H, Liu J, Lin J et al. Uric acid stimulates endothelin-1 gene expression associated with NADPH oxidase in human aortic smooth muscle cells. Acta Pharmacol Sin. 2008 Nov;29(11):1301–1312.
- 31. Şahin E, Deveci İ, Dinç ME et al. Oxidative Status in Patients with Benign Paroxysmal Positional Vertigo. J Int Adv Otol. 2018 Aug;14(2):299–303.
- 32. Musat G. The clinical characteristics and treatment of benign paroxysmal positional vertigo in the elderly. Romanian J Neurol Rev Romana Neurol. 2010 Dec 1;9.
- 33. Dix MR, Hallpike CS. The pathology symptomatology and diagnosis of certain common disorders of the vestibular system. Proc R Soc Med. 1952 Jun;45(6):341–354.
- Mègnigbêto CA, Sauvage JP, Launois R. Validation clinique d'une échelle du vertige: EEV (European Evaluation of Vertigo) [The European Evaluation of Vertigo (EEV) scale: a clinical validation study]. Rev Laryngol Otol Rhinol (Bord). 2001;122(2):95-102. French. PMID: 11715268.
- 35. Talmud JD, Coffey R, Edemekong PF. Dix Hallpike Maneuver. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 [cited 2021 Apr 28].
- 36. Hilton MP, Pinder DK. The Epley (canalith repositioning) manoeuvre for benign paroxysmal positional vertigo. Cochrane Database Syst Rev. 2014 Dec 8;(12):CD003162.
- 37. Hilton MP, Pinder DK. The Epley (canalith repositioning) manoeuvre for benign paroxysmal positional vertigo. Cochrane Database Syst Rev. 2014 Dec 8;(12):CD003162.
- 38. Meclizine. 2021 [cited 2021 May 2].
- 39. Gacek RR. Further observations on posterior ampullary nerve transection for positional vertigo. Ann Otol Rhinol Laryngol. 1978 Jun;87(3 Pt 1):300–305.

40. Rho YH, Zhu Y, Choi HK. The epidemiology of uric acid and fructose. Semin Nephrol 2011; 31: 410–419.

APPENDICES

Appendix I: General information and consent

PARTICIPANT INFORMATION AND CONSENT FORM FOR ENROLMENT IN THE STUDY

Title of Study: Correlation of serum uric acid and BPPV.

Principal Investigator/and institutional affiliation: DR OKINDO CHRISTINE POSTGRADUATE STUDENT, UNIVERSITY OF NAIROBI

Introduction:

I would like to inform you about my study on correlation of serum uric acid levels and BPPV at the KNH. This consent form is aimed at giving you the information you need to enable you to make an informed decision. You will be allowed to ask any questions regarding the study. Where you do not understand the benefits and risks of the study, kindly seek clarification. Upon answering your questions and concerns to your satisfaction, you may decide to be included in the study or not. You shall be required to sign a consent form that you have agreed to voluntarily participate in this study. Note that your decision to participate in this study should be voluntary and you may withdraw from the study if you wish to do so without having to give reasons for your withdrawal.

Refusal to participate in the research will not affect the services your child is entitled to in this health facility or other facilities. We will give you a copy of this form for your records.

May I continue? YES / NO

This study has approval by Kenyatta National Hospital-University of Nairobi Ethics and Research Committee Protocol No.....

WHAT IS THIS STUDY ABOUT?

The researcher listed above is examining you to see if there is any relationship between serum uric acid levels and BPPV. Patients in this research study will be asked basic demographic questions. Participant will undergo assessment of their serum uric acid levels by obtaining a venous blood sample. We are asking for your consent to consider participating in this study.

WHAT WILL HAPPEN IF YOU DECIDE TO BE IN THIS RESEARCH STUDY?

If you agree to participate in this study, the following things will happen: You will be interviewed by the investigator in a private area where you feel comfortable answering questions. The interview will last approximately 15 minutes.

Your will proceed to have a venous blood sample taken for measurement of serum uric acid levels. We will ask for a telephone number where we can contact you if necessary. If you agree to provide your contact information, it will be used only by people working for this study and will never be shared with others. The reasons why we may need to contact you include: clarification on answers provided in the questionnaire.

ARE THERE ANY RISKS, HARMS DISCOMFORTS ASSOCIATED WITH THIS STUDY?

Medical research has the potential to introduce psychological, social, emotional and physical risks. Effort should always be put in place to minimize the risks. One potential risk of being in the study is loss of privacy. We will keep everything you tell us as confidential as possible. We will use a code number to identify you in a password-protected computer database and will keep all your records in a locked file cabinet.

However, no system of protecting your confidentiality can be secure, so it is still possible that someone could find out that you were in this study and could find out information about you. In addition, answering questions in the interview may be uncomfortable for you. If there are any questions you do not want to answer, you can skip them. You have the right to refuse the interview or any questions asked during the interview.

The study will not expose you to any risks except for the slight pain felt while blood is being taken from your vein.

ARE THERE ANY BENEFITS BEING IN THIS STUDY?

We will refer you to a hospital for care and support where necessary. In addition, the information you provide will help us better understand the relationship between serum uric acid levels and BPPV. This might help us to develop other treatment strategies.

WILL BEING IN THIS STUDY COST YOU ANYTHING?

There are no costs to be incurred.

WILL YOU GET REFUND FOR ANY MONEY SPENT AS PART OF THIS STUDY?

There are no refunds as there are no costs.

WHAT IF YOU HAVE QUESTIONS IN FUTURE?

If you have further questions or concerns about participating in this study, please call or send a text message to the study staff at the number provided at the bottom of this page.

For more information about your rights as a research participant, you may contact the Secretary/Chairperson, Kenyatta National Hospital-University of Nairobi Ethics and Research Committee Telephone No. (254-020) 2726300-9. Ext. 44355 email uonknh_erc@uonbi.ac.ke.

The study staff will pay you back for your charges to these numbers if the call is for studyrelated communication.

WHAT ARE YOUR OTHER CHOICES?

Your decision to participate in research is voluntary. You are free to decline participation in the study and you can withdraw from the study at any time without injustice or loss of any benefits.

CONSENT FORM (STATEMENT OF CONSENT)

Participant's statement: I have read this consent form or had the information read to me. I have had the chance to discuss this research study with a study counselor. I have had my questions answered in a language that I understand. The risks and benefits have been explained to me. I understand that my participation in this study is voluntary and that I may choose to withdraw any time. I freely agree to participate in this research study. I understand that all efforts will be made to keep information regarding my child's personal identity confidential.

By signing this consent form, I have not given up any of the legal rights that I have as a participant in a research study.

I agree to participate in this research study:	Yes	No
I agree to provide contact information for follow-up:	Yes	No
Participant printed name:		
Participant signature / Thumb stamp	Dat	te

Researcher's statement

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has willingly and freely given his/her consent.

Researcher's Name : Dr CHRISTINE OKINDO	Date:
--	-------

Signature	
~- <u>B</u>	

Role in the study: _____

For more information, contact,

Dr Mary Omutsani Consultant ENT, Kenyatta National Hospital, (utsani@yahoo.com) TEL-0722672239

Dr John Ayugi, Consultant ENT, University of Nairobi, (johnayugi@gmail.com)-TEL-0722883041

Ms. Serah Ndegwa, consultant audiologist, university of Nairobi(serahndegwa8@gmail.com)TEL-0721310657

Dr Christine Kerubo Okindo, Registrar, ENT, University of Nairobi,chokindo@gmail.com.TEL-0710567145

KNH-UON Ethics research committee;uonknh_erc@uonbi.ac.ke TEL-0721257746

Witness Printed Name (If witness is necessary)

Name ______Contact information _____

Signature /Thumb stamp: _____Date; _____

Appendix II: Fomu Ya Makubaliano

Kiambatisho; Fomu ya Maelezo Kuhusu Idhini ya Wateja

Kitangulizi

Mimi ni daktari christine okindo anayesomea masoma ya juu ya kitengo cha upasuaji wa masikio, mapua, koo, kichwa na shingo katika chuo kikuu cha Nairobi. Ningependa kuomba idhini yako ya kushiriki katika utafiti wenye lengo la kujua kiwango cha asidi ya uric kwenye damu.

Jinsi ya kushiriki

Baada ya wewe kupeana idhini ya kushiriki katika utafiti huu, utafanyiwa uchunguzi zaidi wa kupimwa damu kuamua kiwango cha asidi ya uric kwenye damu. Hakuna gharama yoyote zaidi utakayolipishwa na hakuna madhara yoyote ya kushiriki katika utafiti huu.

Una haki ya kuondoka kutoka kwa utafiti huu wakati wowote bila adhabu yoyote. Utapewa habari kuhusu uchunguzi utakaofanywa na umuhimu wa matokea yatakayopatikana.

Jinsi gani kushiriki kwako kunaweza kuleta madhara?

Utafiti huu hautakudhuru kwa njia yoyote; taarifa yote kuhusu ugonjwa wako utakuwa ni siri.

Je tutafanyia nini matokeo ya utafiti huu?

Maarifa tutakayopata yatasaidia kuboresha huduma itakayopewa kwa mgonjwa wa BPPV.

Kuna uwezekano wa kuchapishwa kwa matokeo ya utafiti huu katika majarida ya kisayansi au kuwakilishwa katika mikutano ya kisayansi na umma kwa jumla bila kuwataja wahusika.

Je umeridhika?

Iwapo umeridhishwa na maelezo uliyoyasoma na kufafanuliwa, tafadhali weka sahihi yako kwenye fomu ya idhini inayofuata:

(ii) Sehemu ya pili – Idhini ya mgonjwa

Mimi (Jina)...... kwa hiari yangu, nimekubali kushiriki katika utafiti huu ambao unafanywa na Daktari Christine Okindo. Nimeelezewa manufaa na madhara ya utafiti huu kwa undani na nimeridhika.

Jina la Mgonjwa.....

Sahihi	 	 	
Tarehe	 	 	

Nambari ya utafiti.....

Kwa maelezo zaidi, wasiliana na

Dr Mary Omutsani Consultant ENT, Kenyatta National Hospital, (utsani@yahoo.com)TEL-0722672239

Dr John Ayugi, Consultant ENT, University of Nairobi, (johnayugi@gmail.com)-TEL-0722883041

Ms. Serah Ndegwa, consultant audiologist, university of Nairobi (<u>serahndegwa8@gmail.com)-</u> <u>TEL-</u>0721310657

Dr Christine Kerubo Okindo, Registrar, ENT, University of Nairobi (chokindo@gmail.com)-TEL-0710567145

KNH-UON Ethics research committee; (uonknh_erc@uonbi.ac.ke)-TEL-0721257746

Jina la shahidi (Ikiwa shahidi ni lazima)

Jina _____maelezo ya mawasiliano _____

Sahihi: ______tarehe: _____

<u>Serum uric acid levels in patients with benign paroxysmal positional Vertigo (BPPV): A</u> <u>case control study at Kenyatta National Hospital</u>.

Appe	endix IIIa: Data Collection Sheet					
Study	y Number	Date			_	
SECT	ΓΙΟΝ A-BIODATA:					
	1.Age (years) 2.	Sex		•		
SECT	FION B-HISTORY					
I.	Have you ever had history of vertigo?	yes	No			
II.	Does looking up increase the vertigo?	Yes	No			
III.	Does the vertigo make you have difficulty YesNo	getting	into or	out	of	bed?
IV.	Do quick movements of your head increase the vertige No	o?		Y	es	
V.	Does bending over increase the vertigo?		Yes	No		
VI.	Any history of nausea during vertigo attacks?		Yes	N	I о	
VII.	Any history of vomiting during vertigo attacks? No			Y	es	
VIII.	How long have you had this condition	?				
IX.	How long ago was the last attack					
Х.	Number of recurrences					
XI.	How long do they last? <1min	>1min	5 mins	5		

SECTION C-VESTIBULAR ASSESMENT TEST FOR BPPV

Dix-Hallpike Maneuver							
Right Ear		Left Ear					
Positive		Positive					
Negative		Negative					

Supine Roll Test							
Right Ear		Left Ear					
Positive		Positive					
Negative		Negative					

FINAL DIAGNOSIS

SECTION D: LABORATORY RESULT

Serum Uric Acid level male (214-488 umol/l) Female (137-363 umol/l)

Serum uric acid levels in patients with benign paroxysmal positional Vertigo (BPPV): A	L
case control study at Kenyatta National Hospital	
Appendix IIIb: Fomu ya kukusanya data	
Nambari ya utafiti Tarehe	
SEHEMU YA A:DATA YA KIBAYOLOJIA:	
1.Umri(miaka)	
SEHEMU YA B:HISTORIA I. Umewahi hisi kizunguzungu? Ndio La	
II. Ukitizama juu hicho kizunguzungu huwa kinaongezeka? Ndio La	
III. Hicho kizunguzungu kinakuzuia kuingia ama kutoka kitandani? NdioLa	
IV. Ukitingisha kichwa kwa haraka huwa inaongeza kizunguzungu? Ndio La	
V. Ukiinama huwa inaongeza kizunguzungu? Ndio La	
VI. Wakati ukona kizunguzungu huwa unapatwa na kichefuchefu? Ndio La	
VII. wakati ukona kizunguzungu huwa unatapika? NdioLa	
VIII. Umekua na huu ugonjwa kwa muda mgani?	
IX. Huu ugonjwa unajirudia mara ngapi?	

X. Mashambulizi ya kizunguzungu hukaa kwa muda mgani <dakika1 >dakika 1 dakika tano

SECTION C-VESTIBULAR ASSESMENT TEST FOR BPPV

Dix-Hallpike Maneuver							
Right Ear		Left Ear					
Positive		Positive					
Negative		Negative					

Supine Roll Test							
Right Ear		Left Ear					
Positive		Positive					
Negative		Negative					

FINAL DIAGNOSIS

SECTION D: LABORATORY RESULT

Serum Uric Acid level male (214-488 umol/l) Female (137-363 umol/l)