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Investigation of plasma electrolyte levels in selected uterine cancer patients

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Abstract:
Background: The balance of electrolytes in humans is not only considered pivotal for normal functioning of cells and organs but to recover from many metabolic disorders. Cancer patients are generally at risk for electrolyte imbalances from a myriad of causes.
Aim: This study was undertaken to estimate electrolytes levels in uterine cancer patients and that of controls (healthy individuals). Clinical parameters were collected after obtaining informed consent from both patients and controls.
Method: Venous fasting blood samples of freshly diagnosed uterine cancer patients and controls were collected to estimate electrolytes namely sodium (Na^+), potassium (K^+), chloride (Cl^-), inorganic phosphate (PO_3^{2-}) and bicarbonate (HCO_3^-). Na, K, Cl and P were analysed spectrophotometrically (colorimetry) while HCO_3^- was biochemically analysed by titration.
Results: Data obtained in this study shows a significant increase ($P<0.05$) in the level of PO_3^{2-} and Na^+ in uterine cancer patients as compared with the control. However, a significant decrease was recorded in the level of Cl^- and HCO_3- in uterine cancer patients when compared with controls. No significant difference in K^+ level was observed in both uterine cancer patients and controls. The evidence of associations between electrolyte imbalances and risk of developing uterine cancer as observed in this study are of particular importance in the prognosis, diagnosis and management of uterine cancer.

Keywords: Electrolytes, Electrolyte Imbalance, Plasma, Uterine Cancer

All co-authors agreed to have their names listed as authors.

1. INTRODUCTION

Uterine cancer is globally acclaimed as the sixth most common cancer in women (fourteenth most common cancer overall), with 320,000 new cases diagnosed in the United States in 2012 [1] [2]. It is the most frequently diagnosed gynaecological cancer among women (aged 55-64 years) and the next rated cause of cancer death among women (after breast cancer) in Nigeria. In the United States, the number of deaths was 4.6 per 100,000 women per year based on 2010-2014 and while, it is estimated that there will be 61,380 new cases of endometrial cancer and an estimated 10,920 people will die of this disease in 2017 [3]

This malignancy develops when normal cells in the uterus or womb suddenly change and grows uncontrollably due to loss of regulation, forming a mass (tumor). Hence, this may develop in cells lining the uterus (endometrium) as *endometrial hyperplasia* and in muscle or other tissues of the uterus as *uterine sarcoma* [4].

Abnormal uterine bleeding generally presages the diagnosis of uterine cancer. In premenopausal women this may present as bleeding between menses or menses which are heavier than usual, pain during urination and sexual intercourse [5][6]. In postmenopausal women, this may present as bleeding, spotting, or an increased vaginal discharge. Treatment of endometrial cancer generally begins with hysterectomy, followed by selective use of radiation and chemotherapy based on findings at hysterectomy and lymph node evaluation, if performed [7]. The risks for uterine cancer are enormous, and this include age, diet, heredity, obesity, diabetes mellitus, breast cancer, late menopause, high levels of oestrogen, pelvic radiation and ethnicity [8][9].

On the other hand, electrolyte disorders are commonly encountered in patients with cancer and can be secondary to either the cancer itself or its therapy [10]. Indeed, electrolytes (e.g. sodium, potassium, etc) play important roles in the normal functioning of human body. They are electrically charged minerals that can be found in body tissues and blood in the form of dissolved salts capable of performing specific physiological functions and thus, they exist within a narrow concentration range in order to express their physiological functions. Their general functions are worthwhile, in that they aid the movement of nutrients into and wastes out of the body's cells, maintain a healthy water balance and pH level of body's fluid and are responsible for muscle functions and other important processes in the body. Required amounts of these elements must however, be in human body and diet to pursue good healthy life [11]. A value higher or lower than the normal range is referred to as electrolyte imbalance. Thus, uncorrected electrolyte abnormalities may have life-threatening sequelae such as kidney failure, paralysis, seizures, coma, intractable nausea and vomiting, diarrhoea, and even death [12]. Tumors that produce adrenocorticotropic hormone also result in water and electrolyte abnormalities [12]. Due to the increasing importance of cancer as a global health problem, the nutritional aspects of cancer metabolism and therapy are now being appreciated, stimulating new research in this direction. Severe caloric restriction lowers basal-specific metabolic rates associated with reduced cancer frequency [13]. The effect of cancer on sodium metabolism is nonspecific while a rise in the total body potassium is an excellent indicator of an anabolic state [14][15].

Diet from plant sources (majorly cereals, fruits and vegetables) and those of animal sources contribute substantially to the electrolyte's level in the body at the point of metabolism. Fruits are known to be excellent source of nutrients such as minerals and vitamins. Sodium, potassium, calcium, chloride and bicarbonate are the major electrolytes in the body of humans.

Potassium (K^+) is one of the most abundant intracellular cations essential for the life of living organism. Its primary physiological functions include regulation of heart contraction and maintenance of body fluid balance. Potassium-rich foods include meats, beans, fruits, vegetables and potatoes. An abnormal increase of potassium (hyperkalemia) or decrease of potassium (hypokalemia) can profoundly affect the nervous system and heart, and when extreme, can be fatal. The normal blood potassium level of 3.5 - 5.0 milli-equivalent (mEq/L) is essential for normal cell function. Potassium together with sodium regulate water and acid-base balance in blood and tissue [16]. Hypokalemia and Hyperkalemia are disorders of potassium imbalances. Hypokalemia is indicated by a very low blood potassium level and Hyperkalemia is indicated by a very high blood potassium level. A pilot study report shows that countries that consume high potassium diets tends to have a lower cancer risks than countries that consumes low potassium diets [17]. Another study reported that patients with hyperkalemic diseases (Parkinson, Addison) usually have reduced cancer rates and patients with hypokalemic diseases (alcoholism, Obesity, stress) have increased cancer rates [18].

Sodium (Na^+), an essential nutrient and a major cation in the extra-cellular fluid found in the plasma is responsible for water homeostasis, nerve and muscle fibre impulse transmission [19] [20]. It also regulates blood pressure and volume. Sodium balance in the body is greatly dependent on the rate of renal sodium excretion. Normal blood sodium level is 135-145mEq/L. Hypernatraemia and hyponatraemia are electrolyte imbalance disorders, characterised by a high level of blood sodium and a very low level of blood sodium respectively. Recent reports suggest that high salt intake can damage the lining of the stomach and might increase the risk of stomach cancer [17].

Chloride (Cl^-) is a major anion responsible for the maintenance of cation/anion balance between intra-and extra-cellular fluids, regulating hydration, osmotic pressure, and acid/base equilibrium. Adult range of blood chloride 97-107 mEq/L. Chloride homeostasis is regulated by anti-diuretic hormone. Low serum chloride level may cause extensive burns, excessive vomiting, intestinal obstruction, nephritis, metabolic acidiosis and addisonian crisis. Elevated chloride level in the body may cause dehydration, hyperventilation, congestive heart valve, uterine obstructions. Chloride balance is maintained by oral, or in emergencies, intravenous (IV) intake of chloride-containing substances. Chloride ions modulate cell proliferation of human androgen-independent prostatic cancer cells [21]. Apoptosis can be induced by facilitating chloride ion transport [22]. Intracellular chloride channels are critical mediators of cell viability and potential targets for cancer therapy [23] this is an intervening evidence of chloride's essentiality in stemming cancer growth.

Bicarbonate (HCO_3^-) is an important electrolyte located in the blood and cells responsible for maintaining the body's acid-base balance. Bicarbonates are necessary for Muscle contraction, nerve function and fluid balance of the body system. Deficiency of bicarbonate may cause muscles cramp, nervous disorders and the most obvious is persistent vomiting and diarrhoea. A recent study reported that drinking sodium bicarbonate could restrict cancer metastasis, and the injection of bicarbonate into tumors could cause cancer regression [24].

Inorganic phosphate (PO_4^{3-}) is a dietary constituent well-known for its role in skeletal mineralization, and normal levels of PO_4^{3-} are essential to maintain normal cellular function [25]. A high PO_4^{3-} diet has been reported to cause a significantly increased development of lung and skin cancers, as well as perturbed normal brain growth in animal studies [26] [27] [28]. Abnormal (PO_4^{3-}) levels are associated with the development of cancer [29]. They are approximately 80% found in the bony skeleton, and 20% distributed in the soft tissues and muscle. Phosphate is the major intracellular anion and shifts between the intracellular and extracellular components. Protein-rich food is a major source of phosphate intake and cereals and nuts. The daily phosphate is about 30 mmol with approximately 80% being absorbed in the jejunum. Its level in serum can be subjected to a rapid change in response to environmental changes such as diet, fluctuation in growth hormone levels, insulin levels and kidney functions. Inorganic phosphates (1.5-2.5mEq/L) are necessary for muscle contraction, nerve function and fluid balance of the body system.

Disturbances of electrolyte metabolism discussed above, if not properly managed, can have potentially life-threatening consequences. The hallmark of effective cancer control is the development of a comprehensive population-based cancer registry, as it provides reliable statistics for comparison of cancer risk between populations. Nigeria has engaged in recent efforts to address the spectrum of non-communicable diseases, and cancer in particular, there is no formal cancer control plan, no standardized screening and early detection programs, and no nationally coordinated population-based cancer registries and more importantly, there is paucity of information on the roles of electrolytes in the pathogenesis and management of uterine cancer [30].

Meanwhile, a substantial proportion of the global burden of cancer could be prevented through the application of existing cancer control knowledge, including tobacco control policies, vaccination (for liver and cervical cancers) and early detection and treatment, as well as public health campaigns promoting physical activity and a healthier dietary intake. In view of the physiological functions of electrolytes in human body and the need to recognize the cause of fluid and electrolyte abnormalities while making treatment decisions, this study was undertaken to investigate the comparative level of plasma electrolytes in patients with uterine cancer against normal subjects (healthy individuals) using appropriate standard methods to estimate the electrolyte level. More so, plasma electrolytes are generally regarded as simple, precise, useful, cheap measurements which it is worthwhile to make as part of a screening procedure and hence, the need for this study [31].

2. MATERIAL AND METHODS

Patients and Study Design

This case-controlled comparative study was carried out in the department of chemical pathology, Obafemi Awolowo University Teaching Hospital (OAUTH), Nigeria. The patients' consent was sought before recruitment into the study. Twenty (20) freshly diagnosed uterine cancer patients (aged 45 – 65 years) confirmed by biopsy and with no other medical complications apart from uterine cancer were selected by convenience sampling. Twenty (20) age-matched uterine cancer-free and healthy volunteers (all females) were used as controls after exclusion of the disease by history and clinical examination. None of the patients or control subjects was on phosphate, calcium, sodium, chloride, bicarbonate and supplements.

Collection of Blood Samples

10 ml of venous fasting blood samples of each of the subjects in each of the subject groups were drawn into lithium heparinised anticoagulant bottle. The blood samples collected were promptly centrifuged at 4000 rpm for 5 minutes. The sputum of each of the subjects in each of the subject groups were collected in a sterile universal bottle.

Estimation of Sodium and Potassium

Plasma obtained after centrifugation of samples was analyzed for sodium and potassium on flame photometer based on the principle of atomic emission spectrometry. A method of Teri et al (1958) was ultilized [32] using Teco Diagnostic 4925e Hunter Ave. Anaheim CA. 92807 Reagent set. Internal standard of sodium and potassium were used each to eliminate interferences due to variations in dilution ratios [33] for reliable results. 10ml of plasma sample, 1000ml of distilled water (i.e. blank) and 5ml of 5ml of internal standard potassium (for potassium only) and internal standard sodium (for sodium only) were used to prepared diluents respectively. Each of these diluents were dispensed into different test-tubes and to each of the labelled test-tubes marked as test, control and standard respectively. Samples were mixed thoroughly and incubated for 10 minutes at 25ºC. The meter reading of the flame photometer was adjusted to zero (0) standard value. The standard was removed and aspirator was dipped into distilled water and equilibrated for 15 minutes. The absorbance of the test, standard and control were read against the reagent blank at 570 nm.

Estimation of Inorganic phosphates

Inorganic phosphate (PO_4^{3-}) was estimated using a method described by Bell and Dolsy (1920) [34]. 10ml of the plasma sample,10ul of distilled water (i.e. blank) were dispensed into test tubes.10ul of the standard inorganic phosphate were added, mixed and centrifuged at 4000 rpm for 5 minutes. The samples were thorough mixing and were incubated for 10 minutes at 20⁰C until colour developed. After incubation, pink colour was observed, indicating that the reaction has taken place. The blank was used to set the spectrophotometer to zero and the absorbance of the samples and standard were read against the reagent blank at 340nm wavelength.

Estimation of Chloride

Chloride ions were estimated using a method of Skeggs and Hochstrasser (1964) [35]**.** 10ml of the plasma sample,10 µl of distilled water (i.e blank) were dispensed into test tubes.10 µl of the chloride reagent were added, mixed and centrifuged at 4000 rpm for 5 minutes and incubated at room temperature for 5 minutes. Spectrophotometer was set-up to 480nm and zero with reagent blank and the absorbance of the samples and standard were read against the reagent blank at 540nm.

Calculation for K^+, Na^+, PO_4^{3-} and Cl^- estimation:

$$\text{Concentration of electrolyte (mmol/L)} = \frac{\text{Absorbance of Test}}{\text{Absorbance of Standard}} \times \text{Concentration of Standard}$$

Estimation of Bicarbonate

Bicarbonate (HCO_3^-) was analysed biochemically using the titration method described by Van Slyke [36]. 1ml of de-ionized water was pipetted into a beaker. 50ul of plasma and 1ml 0f 0.01N HCl were added to the beaker with 1ml of de-ionized water and were mixed thoroughly before a drop of 0.1% phenol Red was added. The resulting components of the beaker were titrated with 0.01N NaOH. After titration at a room temperature, the titre values were recorded.

<u>Calculation</u>

HCO_3^- conc. (mmol/l) = 1000 (ml of acid x N of acid) – (ml of NaOH X N of NaOH)

Data Analysis

Statistical differences among blood plasma electrolytes between study group and control subjects were determined using a two-way ANOVA. The multi-comparison analyses were done using Turkey posthoc test at $p<0.05$, $p<0.01$ and $p<0.001$. All analyses were performed with Graphpad 7 software.

3. RESULT AND DISCUSSION

Figure 1 shows the results for comparison electrolytes level (PO_4^{3-}, Cl^-, Na^+, K^+, HCO_3^-) in the blood plasma samples (mmol/L) of uterine cancer patients and healthy individuals.

There was a significant increase ($P<0.05$; $P<0.0001$) in the level of PO_4^{3-} and Na^+ in uterine cancer patients as compared to the control group respectively. However, there was a significant decrease ($P<0.05$; $P<0.0001$) in the level of Cl^- and $HC0_3^-$ in uterine cancer patients as compared to the control group. There was no significant difference ($P>0.05$) in the level of K^+ in uterine cancer patients as compared to the control group.

Electrolytes are important for the normal physiology of life. The whole body actually acts like a bioelectric organism, and electrolytes are both the switch and the energy source for our body [37]. Fluid and electrolyte abnormalities are not uncommon to patients with malignancy. This is because cancer patients often experience alterations in absorption, distribution and excretion of fluids and electrolytes, and the severity of such complications usually parallel the magnitude of the disorder.

Plasma electrolyte values are usually indicative of the renal functions or dysfunctions. The result of this study has shown that women with uterine cancer have higher plasma phosphate levels when compared with the control subjects. These findings however differ from a similar study on breast cancer patients conducted in Nigeria [38]. Both hyperphosphatemia and high levels of glucose-6-phosphate dehydrogenase and inositol polyphosphate phosphatise (phosphate-enriched enzyme) have also been reported present in other malignancies [39] [40]. The above observation can be attributed to the fact that in cancer cells, there is an uncoordinated cellular metabolism that could lead to cell invasion or gradual destruction of healthy cells and therefore leading to the influx of PO_4^{3-} from the cells to the plasma. Thus, abnormal (PO_4^{3-}) levels are related to development of cancer [29].

Under physiological conditions, most of the Na^+ is reabsorbed in the proximal tubule of the kidney [20]. The same reason for the significant increase of plasma phosphate levels as stated above also holds for the significant increase in sodium level in uterine cancer patients as compared with control subjects. Hence, there is tendency for patients with malignancy to develop abnormal sodium increase (hypernatremia) if their thirst mechanism is defective or if they are unable to drink [10]. This disordered sodium balance is tumor-related and has also be linked to a decrease in true circulating blood volume, sodium absorption interference (causing damage to renal tubules) in a syndrome of inappropriate secretion of antidiuretic hormone (SIADH) [41]. Abnormal decrease of plasma sodium (hyponatremia) is mostly observed in most cancer patients [41] but differences in pathophysiologic mechanisms may drive unique electrolyte disorders in different malignancies [42]. Hence, the reason for the significant increase in uterine cancer patients.

Although disorders of potassium balance are common in patients with malignancy, but so far, no significant difference in potassium levels of study group as compared with the control was observed in this study. Problems with potassium balance may generally result from increased intake or decreased excretion of potassium. Minor changes in potassium level can cause weakness, fatigue and rapid heartbeat. Increased catabolism of body protein leading to the influx of K^+ from the intracellular compartment to the plasma happens often during stress which depends on the severity of the illness [43].

The significant decrease in plasma chloride level in uterine cancer patients against normal subjects could however be due to decreased synthesis or altered catabolism of chloride ions in the body which is not uncommon in patients with malignancies. There is increasing evidence that depletion of sodium chloride in the body may exert a serious neoplasmic effect on the renal electrolyte function [44], and that chloride ions can modulate cell proliferation of human androgen-independent prostatic cancer cells [21]. Similarly, the significant loss of bicarbonate ions in cancer patients is evident in a recent study [45] and can be attributed to the body's compensatory mechanism maintain electrochemical neutrality due to the plasma levels of Na^+ and especially chloride [43].

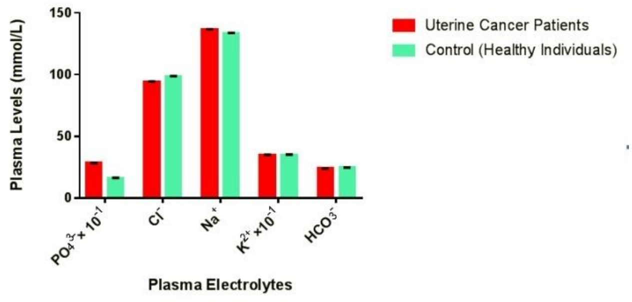

Fig.1: Plasma electrolytes levels in uterine cancer and control subjects

4. CONCLUSION

It was concluded that differences in electrolytes found in uterine cancer patients as compared with healthy individuals may have a great potential as a diagnostic tool in clinical practice. Thus, this study suggests that development of electrolyte abnormalities is likely to provoke symptoms that can negatively affect quality of life and may prevent certain chemotherapeutic regimens. Early recognition of a probable spurious electrolyte test result and early diagnosis of uterine cancer and familiarity with the possible causes could help circumvent potentially harmful interventions or long termed complications. The authors therefore recommend a larger study with a greater range of values to further define the strength of this relationship. Further studies in this field should take into account the hormonal and metabolic factors involved in electrolyte metabolism and also the role of dietary electrolyte intake, while also addressing the impacts of other cancer-related effect modifiers beyond the coverage of the current study.

Limitations of the Study

Anthropometric and blood pressure data for the patients were not obtained.

ETHICAL APPROVAL

We got informed consent from the patients and ethical committee of the Obafemi Awolowo University Teaching Hospital (OAUTH), Nigeria, approved this study.

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