

**MAGNITUDE OF HYPOPHOSPHATEMIA IN CHILDREN
UNDER FIVE YEARS WITH KWASHIORKOR AND
MARASMIC KWASHIORKOR AT KENYATTA
NATIONAL HOSPITAL**

**A DISSERTATION SUBMITTED IN PART FULFILLMENT FOR
THE DEGREE OF MASTERS IN MEDICINE (PAEDIATRICS AND
CHILD HEALTH) OF THE UNIVERSITY OF NAIROBI.**

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DECLARATION


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DEDICATION

To my late mother Rael Toiyoi, who worked tirelessly

to provide me with formal education.

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LIST OF ABBREVIATIONS

Adm.	-	Admission
ATP	-	Adenosine triphosphate
CI	-	Confidence interval
DPG	-	Diphosphoglycerate
GE	-	Gastroenteritis
g/l	-	Grams per litre
HIV	-	Human immunodeficiency virus
IV	-	Intravenous
Kcal	-	Kilocalories
KDHS	-	Kenya Demographic and Health Survey
Kg	-	Kilogram
KNH	-	Kenyatta National Hospital
mg/dl	-	Milligrams per decilitre
mmol/l	-	Millimoles per litre
mo	-	Months
N	-	Sample size
n	-	Number of cases
PEM	-	Protein Energy Malnutrition
PFC	-	Paediatric Filtering Clinic
P _i	-	inorganic phosphorus
SPSS	-	Statistical Package for Social Sciences
TEN	-	Transpyloric Enteral Nutrition
UoN	-	University of Nairobi
UTIs	-	Urinary Tract Infections
W/A	-	Weight for age
Wgt	-	Weight
WHO	-	World Health Organization

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SUMMARY

Background: A number of biochemical changes in blood and tissues have been described in protein-energy malnutrition (PEM), the main one being electrolyte depletion. Hypophosphatemia is the main feature of refeeding syndrome. It is a recognized cause of morbidity and mortality among children with severe malnutrition. Worldwide, data on prevalence of hypophosphatemia in children with severe PEM is scanty, and especially so in developing countries which bear the highest burden of childhood malnutrition.

Methodology: We carried out a short longitudinal survey at Kenyatta National Hospital (KNH) Paediatric wards to determine the frequency of hypophosphatemia in children under 5 years of age with kwashiorkor and marasmic kwashiorkor, before and during nutritional intervention and to relate hypophosphatemia to outcome in the first week.

Subjects were recruited on admission into the wards. Consecutive sampling of children with kwashiorkor and marasmic kwashiorkor whose mothers/ guardians gave informed consent and met the inclusion criteria was carried out. Blood samples were taken on admission, then days 1, 2 and 4 thereafter. Serum phosphate level was determined on all the four days but serum albumin, calcium and magnesium levels were only determined on admission. Demographic, clinical and laboratory data were collected. Hypophosphatemia was defined as serum phosphate level below 1.20 mmol/l and severe hypophosphatemia as serum phosphate level below 0.33mmol/l.

Results: A total of 165 children were enrolled into the study between June 2005 and February 2006. Of the 165 children, 107 (64%) had kwashiorkor and 58 (36%) had marasmic kwashiorkor. They were of mean age 20 months (range, 3 - 60 months), and majority, 95 (58%) were male.

The prevalence of hypophosphatemia was 86% on admission, increased to 90% on day one and 93% on day two, and then declined slightly to 90% on day four. The prevalence of severe hypophosphatemia was 6% on admission, increased to 18% on day one and 22% on day two, and then declined to 11% on day four. On admission, mean serum

phosphate level was below normal at 0.91mmol/l, declined significantly to 0.67mmol/l and to a nadir of 0.63mmol/l on the first and second day after treatment initiation respectively, then rose slightly to 0.75mmol/l on the fourth day ($p < 0.001$ comparing each follow-up mean level with the admission level). There was a positive association between severity of nadir serum phosphate level and mortality. There were no deaths among children with normal nadir serum phosphate levels. However, among children with mild, moderate and severe hypophosphatemia 8%, 14% and 21% died respectively ($p = 0.028$). There was no significant association between hypophosphatemia and the various demographic, clinical and laboratory correlates. However, those children with dermatosis and hypomagnesaemia showed a trend for association ($p = 0.082$ and 0.099 respectively).

Conclusion: Hypophosphatemia is frequent among children with kwashiorkor and marasmic kwashiorkor presenting at KNH. Phosphate levels decline significantly during the first two days following nutritional intervention, and severity of hypophosphatemia is positively associated with mortality.

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1.0 INTRODUCTION AND LITERATURE REVIEW

Nutritional deficiencies constitute a major public health problem in the tropical and subtropical regions of the world. Among them, protein energy malnutrition (PEM) is the most widespread condition. It mostly affects children under 5 years of age, as their nutritional requirements are relatively higher than those of adults¹. PEM, first described in 1920s, is observed most frequently in developing countries. Marasmus results from inadequate intake of proteins and calories, whereas kwashiorkor results from inadequate protein intake with a fair to normal caloric intake. Marasmic kwashiorkor has features of both groups.

PEM has long lasting effects on growth, development, learning, social adjustment, working efficiency, labour productivity and mortality in childhood¹. On the basis of low weight for age (W/A), WHO estimates that approximately 150 million out of 555 million (27%) children younger than 5 years in developing countries are malnourished. On the basis of low height for age, an additional 200 million children have stunting secondary to poor nutrition². In Sub Saharan Africa, 30% of children have PEM. In Africa, the estimated prevalence of severe PEM ranges between 1.7 –9.8%¹. According to the Kenya Demographic Health Survey (KDHS) of 2003, 20% of children below 5 years of age are underweight and 4% are severely underweight³.

Mortality in kwashiorkor remains high. Infections exacerbated by underlying cellular immunodeficiency contribute to the high mortality. Electrolyte imbalance with ongoing diarrhoea is also problematic⁴. Children admitted with PEM have other disease conditions as well. The most commonly encountered co-morbidities are pneumonia, malaria and urinary tract infections (UTIs) according to a KNH study⁵.

In both children and adults, the first step in the treatment of PEM is to correct hypoglycaemia, fluid and electrolyte abnormalities, to keep the child warm and to treat any infections. Macronutrients are supplied by dietary therapy, the amount of energy is gradually increased during the first week from 80-100 kcal/kg/day to full rates providing

180-200kcal/kg/day. Proteins are started at 0.6-1g/kg/day and increased gradually to 2.9-3.8g/kg/day during rehabilitation phase^{6,7,8}. Various studies have well demonstrated that a normal metabolic mixture (meaning a diet containing minerals, electrolytes, and nitrogen in proportion to their content inside normal cells), in conjunction with adequate calories, is mandatory for the normal repair of the tissues⁹. In addition to the macronutrients, WHO recommends addition of minerals and vitamin mixes to its formula diets for the severely malnourished children. The mineral mix contains potassium, sodium, magnesium, zinc, selenium and copper¹⁰.

In developing countries, approximately 50% of the 10 million deaths each year are secondary to malnutrition in children under 5 years¹¹. Deaths especially in the first week of treatment are usually due to electrolyte imbalance, infection, sepsis, hypoglycaemia, hypothermia, or heart failure; and they occur in spite of adequate attention to these usual complications^{6,12,13}.

Despite improved medical care, mortality of children with severe PEM remains high at 10-20%¹². Mortality in Kwashiorkor is reported by Fechner et al to range between 10% and 50%¹⁴. This high mortality is mainly found in Sub Saharan Africa despite implementation of standard treatment protocols¹³. Observations from the Paediatric Emergency Ward at KNH showed that malnutrition accounted for 7% of admissions and 15% of mortality¹⁵. This excludes the mild and moderately severe cases that are treated elsewhere as outpatients. Kiaira et al at KNH, found an overall mortality of 10% within the first 5 days⁵.

A number of biochemical changes in the blood and tissues have been described in PEM¹. These changes vary with the severity of malnutrition as well as the type of malnutrition. Electrolytes, especially potassium and magnesium, are depleted; levels of some enzymes and circulating lipids are low, and blood urea decreases⁹. The most common electrolyte abnormalities are hypophosphatemia, hypokalemia and hypomagnesaemia, and they have been associated with mortality in the initial days of treatment^{6,11}.

Phosphorus is an essential macromineral generally found in the human body as part of the phosphate anion of which 80% is intracellular and principally in the bone. 15% of body phosphate forms intracellular components such as nucleic acid, co-enzymes and phospholipids^{9, 16, 17}. In the phospholipids, phosphate is a structural component of cellular membranes. More importantly, phosphate is involved in the energy pathways of the cell. Phosphate plays an important role in delivery of oxygen to tissues and is part of an important urinary buffer system permitting excretion of fixed acids. Though it is available in most foods, it tends to be depleted in certain disease states like malnutrition. Approximately 800mg of phosphorus on average is the recommended daily allowance for normal children. Dietary sources of phosphorus include protein-rich foods, cereals, and nuts¹⁷.

In children, the concentration of inorganic phosphorus in serum varies between 1.20mmol/l - 2.30mmol/l. In normal individuals, serum phosphorus is regulated within a fairly narrow range. It tends to decrease slightly after ingestion of carbohydrates or fats. During modest respiratory alkalosis, it may decline approximately by 0.16mmol/l. In contrast, serum phosphorus may increase during states of dehydration, and transiently after exercise⁹. Hypophosphatemia associated with infection has been demonstrated in adult patients with early sepsis, pneumonia or other bacterial infections^{18,19}.

A variety of conditions and drug therapies are associated with hypophosphatemia. They include: starvation, osteomalacia, pregnancy, vitamin D deficiency, haemodialysis, pharmacological phosphate binders administration, insulin administration, diuretic therapy, recovery from severe burns and diabetes mellitus⁹. Deficiency of vitamin D depresses calcium absorption from the gut and in addition, decrease parathormone responsiveness of bone. Overproduction of parathormone occurs and this leads to phosphaturia. Diabetics who develop glycosuria, ketonuria and polyuria almost invariably lose phosphate excessively in the urine. Similarly, serum phosphorus concentration may decline as a result of pharmacological diuresis.

Hypophosphatemia has again become a topic of concern. This is due to automation of laboratory measurements which has revealed hypophosphatemia to be common and to occur under a variety of circumstances. Secondly, there is increasing evidence that hypophosphatemia may be associated with serious morbidity⁹. Phosphorus deficiency can result in anorexia, impaired growth, skeletal demineralisation, proximal muscle atrophy and weakness, cardiac arrhythmias, respiratory insufficiency, increased erythrocyte and lymphocyte dysfunction, susceptibility to infections, rickets, nervous system disorders and even death²⁰. However, signs and symptoms rarely occur unless serum phosphorus concentration is $< 0.33\text{mmol/l}$, the usual cut off for severe hypophosphatemia.

Hypophosphatemia, with or without phosphorus deficiency, is found commonly in patients being therapeutically refeed after severe weight loss⁹. The refeeding syndrome is a constellation of abnormalities observed during refeeding of patients with severe protein energy malnutrition. The main abnormalities are the presence of hypophosphatemia, hypokalemia and hypomagnesemia. Most observations on this entity were made by military physicians on prisoners of war in Europe and Asia at the conclusion of World War 2.

Clinically refeeding syndrome presents with neuromuscular, haematological and renal manifestations. The development of this syndrome is associated with high mortality. It is seen when carbohydrates are introduced after a period of malnutrition. Identifications of patients at risk (anorexia nervosa, chronic alcoholism, chronic malnutrition, elderly patients, oncology patients), the introduction of cautious progressive nutrition and careful monitoring of vital signs, electrolyte levels and fluid balance are essential for prevention of morbidity and mortality from this syndrome²¹.

In starvation, serum phosphorus concentration generally remains normal, but may decline to or slightly below the lower range of normal⁹. Starvation leads to the catabolic release of phosphate from intracellular stores, so that normal serum phosphate levels are maintained. The released phosphate is subsequently lost in the urine. Hence, in starvation significant total body phosphate depletion occurs despite normal serum phosphate levels

¹⁶. The sudden shift of phosphate from the extracellular to the intracellular compartment is the predominant etiologic mechanism in most cases of clinically significant hypophosphatemia during refeeding. This follows carbohydrate intake hence release of insulin which stimulates cellular uptake of glucose, phosphate and water⁷. The resulting hypophosphatemia can be profound, especially in patients who already have a substantial total body phosphate deficit ¹⁶.

Severe hypophosphatemia (<0.33mmol/l) has been reported to occur in 0.8% of all hospitalised adult patients²². In a study to assess the tolerance to transpyloric enteral nutrition (TEN) and the incidence of secondary complications in critically ill children, hypophosphatemia was noted to be one of the complications ²³. In a study done locally, Chomba et al. found a low mean serum phosphate in all the PEM patient groups on admission as compared to controls. The lowest mean serum phosphate level of 1.18 mmol/l was found in the patients with kwashiorkor as compared to a mean serum phosphate level of 1.58mmol/l found in the control group ¹⁰. In a study of the incidence of hypophosphatemia in patients with nutritional recovery syndrome, 5 out of 9(56%) had hypophosphatemia (P<0.97mmol/l). Thus the conclusion that all patients with significant malnutrition should be evaluated for this complication of refeeding ⁴.

Internal redistribution in refeeding occurs following stimulation of glycolysis which forms phosphorylated glucose compounds, thus an associated intracellular phosphate shift. Therefore, overzealous hyperalimentation by parenteral or oral routes with phosphate-deficient preparations in chronically malnourished but stable patients can precipitate acute severe hypophosphatemia: with subsequent acute cardiac decompensation, acute respiratory failure, seizures, coma and death ¹⁶. Support for the role of hypophosphatemia comes from the findings that decreased ventricular stroke work and mean arterial pressure, as well as severe congestive cardiomyopathy, have been associated with hypophosphatemia in man²⁴. The most common cause of hypophosphatemia in a general hospital population was found to be intravenous administration of glucose (40/100 cases). In view of this, serum phosphate levels should

be documented as normal before administration of glucose and rechecked frequently during the early refeeding period²⁴.

Refeeding hypophosphatemia is a recognized cause of morbidity and mortality in adolescents with anorexia nervosa but has been rarely reported in younger children with other diagnoses²⁵. In one series of hospitalised adolescents with anorexia nervosa, refeeding hypophosphatemia occurred in 7%²⁶. Friman et al found that 10%(6 of 60) of children presenting with kwashiorkor in South Africa had severe hypophosphatemia and that the metabolic disturbance was associated with dehydration and death²⁷.

Severe hypophosphatemia (serum phosphate <0.33mmol/l), occurred in 8 out of 68 (12%) of children with kwashiorkor within 48 hours of admission, 5 out of the 8(63%) children died compared with 13 out of 60(22% without severe hypophosphatemia (p<0.02). Therefore it was concluded that severe hypophosphatemia seems to be common and life threatening in children with kwashiorkor.²⁸ In the same study, dermatosis and dehydration were significantly correlated with severe hypophosphatemia but these clinical signs could not reliably predict fatal outcomes.

Mezoff et al described five children with PEM who developed asymptomatic refeeding hypophosphatemia²⁰. Two of the episodes of refeeding hypophosphatemia in their paediatric patients occurred within 24 hours. In parts of the world that are impoverished, severe PEM in children is more common and so probably is refeeding hypophosphatemia. Mezoff et al therefore, concluded that the condition is probably underappreciated. A systematic literature review revealed 27 children that developed refeeding syndrome after oral/ enteral feeding. Of these, 9 died as a direct result of complications of this syndrome⁷.

From a systematic literature review, most instances of refeeding syndrome were treated with a reduction in volume and caloric density of the feeds⁷. Thereafter, supplementation of feeds with phosphates and vitamins was instituted and serum phosphate levels of >1.20mmol/l maintained. Oral, enteral or parenteral phosphorus has been used as

replacement therapy in hypophosphatemia^{7,9,29}. Associated with hypophosphatemia are cardiac arrhythmias and delirium. Cardiac events are especially common in the first week and therefore justifying close monitoring of electrolytes and cardiac status²². Goals regarding this metabolic imbalance therefore includes: identifying patients at risk; providing adequate assessment; interdisciplinary care plans and adequate follow up with an emphasis on monitoring and intervention where necessary³⁰.

2.0 STUDY JUSTIFICATION AND OBJECTIVES

2.1 Research Question

What is the prevalence of hypophosphatemia in children under 5 years of age with kwashiorkor and marasmic kwashiorkor presenting at KNH before and after nutritional intervention? Does hypophosphatemia affect outcome in the first week of treatment?

2.2 Study justification

Hypophosphatemia is an underappreciated biochemical imbalance that occurs during nutritional repletion of patients with significant sub optimal caloric intake and it has a potential to cause considerable morbidity and mortality³⁰. Severe hypophosphatemia specifically is associated with acute respiratory decompensation, cardiac arrhythmias and heart failure.

According to the 2003 Kenya Demographic Health Survey (KDHS), an estimated 20% of children less than 5 years of age are underweight with 4% being severely underweight. Kwashiorkor and marasmic kwashiorkor patients are one group of patients at risk of developing hypophosphatemia²¹. Quantifying the problem among them locally is important, as it will form a basis for intervention targeting this high-risk group. Quantification will include both the prevalence of hypophosphatemia at presentation and during the first five days after commencing therapy, the time at which they are thought to be most vulnerable to this complication.

Worldwide, there is paucity of data on refeeding syndrome in children with kwashiorkor as compared to other conditions like anorexia nervosa and intensive care patients. Locally, there is no data on this syndrome. Data collected from this study, therefore, will be useful for future management of such patients and will form a basis for further research especially in all groups of patients who are at risk of developing this syndrome.

2.3 Study utility

The results of this study will guide clinicians on the aspects of prevention and treatment of hypophosphatemia which should be considered as a potential complication in any patient recovering from a period of sub optimal nutrition⁷. The initial clinical and laboratory evaluation of these children will be analysed and used to predict children who are most likely to develop hypophosphatemia and death. Subsequent serial serum phosphate measurement will estimate the critical time during which severe hypophosphatemia occurs and therefore guide on timing of laboratory investigations.

A cautious progressive approach to nutritional therapy has been suggested as an important preventive measure against hypophosphatemia^{7,8}. The results of this study will provide information on the prevalence of hypophosphatemia while using the current malnutrition feeding regimen and hence inform the formulation of future feeding guidelines. The results will form a basis for phosphate replacement therapy as has been suggested in literature. This is especially so in situations of acute severe hypophosphatemia which has been associated with considerable morbidity and mortality resulting from refeeding^{7,9,24}.

2.4 Objectives

2.4.1 Overall Objective

To determine the magnitude of hypophosphatemia in the under fives with kwashiorkor and marasmic kwashiorkor presenting at KNH before and during nutritional intervention and to relate it to outcome in the first week of treatment.

2.4.2 Primary Objectives

1. To determine the prevalence of hypophosphatemia in the under fives with kwashiorkor and marasmic kwashiorkor presenting at KNH.
2. To assess the trend of phosphorus blood levels during the first 5 days of nutritional intervention.

2.4.3 Secondary Objective

1. To relate the level of hypophosphatemia to outcome during the first week of nutritional intervention.

2.5 Ethical consideration

Approval to carry out the study was obtained from KNH Ethics and Research Committee (Appendix IV). The mothers/guardians of eligible children were informed of the study in a language they understood best. The expectations of the study participation, blood sampling and laboratory analysis were explained. The risks and benefits of the study were explained and confidentiality was assured. A written informed consent was obtained following their acceptance to participate in the study (Appendix I).

2.6 Dissemination of results

The results of the study will be distributed to the university library and the department of Paediatrics and Child Health, University of Nairobi. The results will also be presented in scientific conferences and published in scientific journals.

3.0 METHODOLOGY

3.1 Study Design

This was a short longitudinal survey.

3.2 Study Area

The study was carried out in the general paediatric wards of KNH, a teaching and national referral hospital located in Nairobi, the capital city of Kenya. KNH also serves as the main inpatient hospital for the low and middle level income earners in Nairobi and its environs. There are currently four general paediatric wards at the hospital and each admits approximately 30 – 50 patients daily. Severe malnutrition accounts for about 7% of admissions and up to 15% of mortality¹⁵. This study was done in the period between June, 2005 and February, 2006.

3.3 Sample size calculation

Sample size was calculated using the following formula for prevalence studies.

$$N = \frac{Z^2(1-a) P(1-P)}{D^2} \quad , \text{ where}$$

N = sample size

P = Estimated prevalence of severe hypophosphatemia

D = The desired width of the confidence interval.

$Z^2(1-a)$ = The square of the standard normal deviation corresponding to a confidence interval (CI) of 95%.

The prevalence of severe hypophosphatemia in children with kwashiorkor was found to be 12% in Malawi in 1998, and from this information, the prevalence of 12% was used for the computation of the sample size²⁸.

Assumptions

Power of the study is 80%.

Margin of error is 5%.

$$N = \frac{1.96^2 \times 0.12(1-0.12)}{0.05^2}$$

= 162 (165 children were recruited)

3.4 Sampling method

Consecutive sampling of subjects meeting the inclusion criteria was done until the sample size was achieved.

3.5 Study Population

3.5.1 Inclusion criteria

1. All under fives with kwashiorkor and marasmic kwashiorkor.
2. All under fives whose mothers consented to participate in the study.

3.5.2 Exclusion criteria

1. All children diagnosed to have rickets or diabetes mellitus.
2. Children on antacids, diuretics or insulin treatment at admission or during follow up.
3. All children whose mothers declined or were unable to give informed consent.

3.5.3 Clinical definitions.

1. Kwashiorkor: defined using Wellcome classification as children with 60- 80% of standard body weight-for-age (W/A) with oedema (AppendixIII).
2. Marasmic kwashiorkor: defined using Wellcome classification as children with less than 60% of standard body W/A with oedema.
3. Phosphate levels in children.^{6, 25, 31}
 - Normal range : 1.20 – 2.30 mmol/l
 - Hypophosphatemia: <1.20mmol/l
4. Degrees of hypophosphatemia^{6, 25, 31}
 - Mild : 0.8 - 1.19mmol/l
 - Moderate : 0.33- 0.79mmol/l
 - Severe : <0.33mmol/l

3.6 Clinical Procedures

The investigator visited the study area daily from 8.00 am to 5.00 pm to personally examine and recruit study subjects, and collect blood samples. Each patient's name, ward and hospital number were recorded. Demographic data of each subject were recorded. The initial evaluation included a complete history and physical examination. The patients' clinical notes were checked to see whether they had received glucose using the intravenous route in the Paediatric Filter Clinic (PFC) or at admission into the ward.

A general examination was done and weight was measured and recorded. Level of dehydration and the presence of dermatosis were assessed and recorded. The following infectious disease conditions as diagnosed by the primary clinicians were noted: meningitis, pneumonia, otitis media, gastroenteritis, urinary tract infection (UTI), malaria and human immunodeficiency virus (HIV). These infections tend to be common and complicate PEM^{5,8}. Infections and other co-morbidities, as diagnosed by the attending clinicians at admission or during the first week were recorded. Children diagnosed by the attending clinician at admission or thereafter, to be affected with rickets or diabetes mellitus were excluded from the study.

Based on the low weight for age charts, the children were classified according to the Wellcome classification (Appendix III). Patients under 5 years falling in the kwashiorkor and marasmic kwashiorkor groups were eligible for inclusion. Patients falling in the underweight or marasmus groups were omitted since there were no specific studies that have assessed this condition in these malnutrition groups. Afzal et al in their extensive literature review, found only 27 children reported to have developed refeeding syndrome following enteral nutrition⁷. More than half of these children had kwashiorkor while the rest had anorexia nervosa as the underlying nutritional disorder. Following this initial evaluation, informed consent in writing (Appendix I) was sought from mothers/guardians whose children qualified.

During this initial contact, the first sample of blood was collected. A 2 millilitre (ml) syringe and gauge 23 needle were used under aseptic technique and application of

negative pressure to draw 2 mls of blood from a peripheral vein. The sample was then placed in a labelled plastic container with a cover for transportation to the laboratory. Firm pressure was applied to the puncture site for about 3 minutes to avoid bleeding. The samples were promptly transported to the Renal Unit laboratory, located within the hospital for analysis. Blood sampling was done serially on day 0 (admission), day one, day two and day four.

3.7 Patient Follow-up

In the wards, the patients were managed for malnutrition by the ward clinicians according to the hospital guidelines. This entailed the use of special milk which is a mixture of cow's milk, sugar, corn oil and eggs that contains approximately 100 Kcal/dl when ingested. The starting volumes usually were 100mls/kg/day divided into eight equal 3 hourly feeds. Infections and other co-morbidities were managed routinely following the usual hospital guidelines. These children were given other supportive treatment like multivitamins and their rooms were kept warm and alternate day weighing was done. The patients were reviewed every morning up to seven days and outcome recorded as either 'Alive' or 'Died' at one week post-admission. For those who died, the duration from admission to death was recorded.

Recruited children were identified using a study number and their in-patient number for confidentiality. The data obtained was stored carefully and regular feedback given to the parents and with their permission, relevant clinical and laboratory findings were passed on to the attending clinicians to help with decision making during patient management. The investigators fully participated in the management of these children. Emergency care and resuscitation took priority during the study. No major complications attributable to the study procedures were recorded during the study period.

3.8 Laboratory Investigations

Serum was separated within two hours to avoid haemolysis and thereafter analysed using the automated method by a qualified laboratory technologist. The Biochemistry analyser Technicon RA 1000, was used. This analyser uses the principle that inorganic phosphorus reacts with ammonium molybdate in the presence of sulphuric acid to form a phosphomolybdate complex, which is measured calorimetrically at wavelength 340 nm. The intensity of the colour is directly proportional to the concentration. Serum phosphorus was measured on admission, day 1, day 2 and day 4. However, serum albumin, calcium and magnesium were measured only on admission.

3.9 Data Management

3.9.1 Data analysis

All the data generated from the clinical and laboratory procedures were recorded into a data form (Appendix II) and then entered into a personal computer Excel worksheet. This was then exported to Statistical Package for Social Sciences (SPSS) Software for analysis. Descriptive statistics including age, sex, hydration status, presence of diarrhoea, presence of infection, presence of dermatosis and intravenous glucose administration were determined and used to describe the demographic and clinical characteristics of the study population.

Students t test was used to compare continuous variables whereas the Chi-square test, Fisher's Exact test and Chi-square for linear trends were used to compare categorical variables. P values ≤ 0.05 were regarded as significant. The outcome from the study was defined as a child's death or survival to 7 days post admission. Results are displayed using frequency tables, bar and line graphs as appropriate.

4.0 RESULTS

A total of 165 children were enrolled into this short longitudinal survey done between June, 2005 and February, 2006. Using the Wellcome classification, each subject was placed in either kwashiorkor or marasmic- kwashiorkor group.

4.1 Demographic and clinical characteristics of the study population.

Males comprised 58% (95 of 165) and females 42%(70 of 165) with a male to female ratio of 1.4: 1. The mean age of the children in the study was 20 months overall with 23 and 19 months mean ages for kwashiorkor and marasmic kwashiorkor respectively. The age range was 3- 60 months (Table 1).

Table 1: Demographic and clinical characteristics of the study population.

Characteristics		Number (n) (%)
Sex	Males	95 (58%)
	Females	70 (42%)
Age (months)	Mean (Range)	20 (3-60)
Class of Malnutrition	Kwashiorkor	107 (64%)
	Marasmic- kwashiorkor	58 (36%)
Hydration status	Dehydration	104 (63%)
Duration of Diarrhoea	No diarrhoea	71 (43%)
	Acute	60 (36%)
	Chronic	34 (21%)
Presence of Infection	Yes	134 (81%)
Presence of dermatosis	Present	62 (38%)
IV Glucose given	Yes	46 (28%)

Majority of the children, 104 of 165 (63%), had some dehydration. Most children, 93 of 165 (56%) had diarrhoea as opposed to 71 of 165 (43%) with no diarrhoea. The majority of those with diarrhoea, 60 of 93 (65%), had the acute form. Infection was diagnosed in most children, 134 of 165 (81%) having at least one type of infection. Dermatitis was present in only 62 children (38%). Majority of children, 119 of 165 (72%), were not given IV glucose (Table 1).

Table 2: Admission (Day 0) biochemical characteristics of the study population.

Characteristic	N	Mean (Range)	SD
Phosphorus (mmol/l)	165	0.9 (0.1 – 2.0)	0.3
Albumin (g/l)	165	26 (10 – 44)	9
Calcium (mmol/)	165	2.1 (1.3 –3.2)	0.4
Magnesium (mmol/l)	165	0.6 (0.1 – 1.2)	0.2

The levels of phosphorus, albumin, calcium and magnesium were all done on admission and their means calculated. All the means were noted to be below the normal ranges for the age at baseline except magnesium which is on the lower end of normal (Table 2).

4.2 Prevalence of hypophosphatemia in children on admission and during follow up.

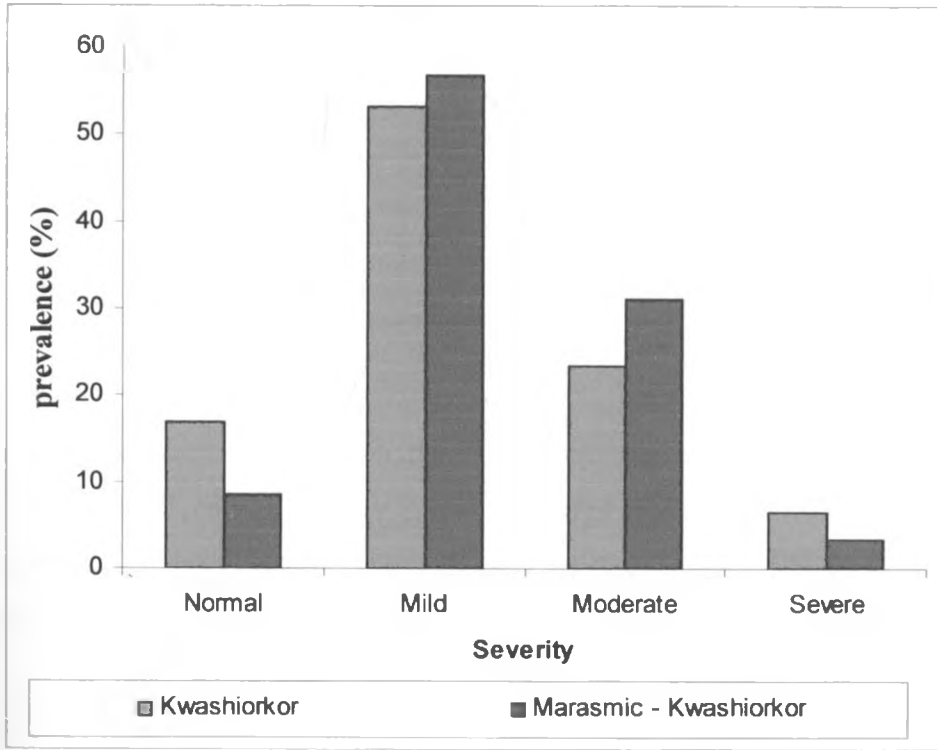
Serum phosphate level at presentation was used to categorize all the children into either normal (≥ 1.20 - 2.30 mmol/l), mild (≥ 0.80 - 1.19 mmol/l), moderate (≥ 0.33 - 0.79 mmol/l) or severe (< 0.33 mmol/l) hypophosphatemia (Appendix III).

Table 3: Prevalence of hypophosphatemia at presentation .

	All patients n (%)	Kwashiorkor n (%)	Marasmic kwashiorkor n (%)	p-value
Normal phosphate	23 (14%)	18 (17%)	5 (9%)	
Hypophosphatemia (subtotal)	142 (86%)	89 (83%)	53 (91%)	0.166
Mild	90 (54%)	57 (53%)	33 (57%)	
Moderate	43 (26%)	25 (23%)	18 (31%)	
Severe	9 (6%)	7 (7%)	2 (3%)	
Total	165 (100%)	107 (100%)	58 (100%)	

On admission, out of 165 children, 142 had hypophosphatemia, giving a prevalence of 86%. The degree of hypophosphatemia was further classified. Of the 165 children, 90(54%) had mild hypophosphatemia, 43(26%) had moderate hypophosphatemia, and 9(6%) had severe hypophosphatemia. Only 23 of the 165 (14%) children had normal phosphate levels. There was no statistically significant difference in the prevalence of hypophosphatemia between kwashiorkor and marasmic kwashiorkor children, P-value = 0.166 (Table 3).

Figure 1: Admission (Day 0) prevalence of hypophosphatemia between kwashiorkor and marasmic kwashiorkor.



Prevalence of hypophosphatemia between the two classes of malnutrition was similar as shown in figure 1 above. The two groups were therefore subsequently treated as one during data analysis.

Table 4: Prevalence of hypophosphatemia during nutritional intervention.

		Day 0	Day 1	Day 2	Day 4
		n(%)	n(%)	n(%)	n(%)
Normal Phosphate		23 (14%)	16 (10%)	11 (7%)	15 (10%)
Hypophosphatemia	Mild	90 (54%)	45 (28%)	44 (28%)	52 (34%)
	Moderate	43 (26%)	71 (44%)	68(43%)	68 (45%)
	Severe	9 (6%)	29 (18%)	35(22%)	17 (11%)
Subtotal		142 (86%)	145(90%)	147(93%)	137(90%)
Total		165 (100%)	161 (100%)	158 (100%)	152 (100%)

During nutritional intervention, the overall prevalence of hypophosphatemia increased to 90% on day 1, to 93% on day 2, and decreased slightly to 90% on day 4. Prevalence of severe hypophosphatemia tripled to 18% on day 1, increased to 22% on day 2, and declined to 11% on day 4 (Table 4).

4.3 Trends in serum phosphate levels during the first 5 days.

Phosphorus levels were measured on each of the 4 days and means calculated. Paired t test was used to establish whether there was any significant difference between the means of the phosphate levels on the various days.

Table 5: Mean phosphate levels during the first five days in the hospital.

Day	n	Mean Phosphate(Range) (mmol/l)	P-value
0	165	0.91 (0.05-1.97)	-
1	161	0.67 (0.08-1.43)	<0.001
2	158	0.63 (0.05-1.40)	<0.001
4	152	0.75 (0.09-1.70)	<0.001

The mean serum phosphate level dropped from 0.91 mmol/l to 0.67 mmol/l after 24 hours. The mean serum phosphate level further dropped to its lowest level of 0.63 mmol/l on day 2. The mean serum phosphate level thereafter rose to 0.75 mmol/l on day 4. The means of days 1, 2 and 4 were compared with admission mean and there was statistical significance in all the days, P value < 0.001. Further comparison between day 1 and 2 showed a significant drop, P value 0.008; and between day 2 and 4 which showed a significant increase, P value <0.001 (Table 5).

The mean nadir on day 2 coincided with the day most children had their lowest serum phosphate. On this day, 78(47%) children had their nadir serum phosphate as compared to 35(21%), 36(22%) and 16(10%) on day 0, day 1 and day 4 respectively.

Figure 2: Trends of mean serum phosphate during follow up by class of malnutrition.

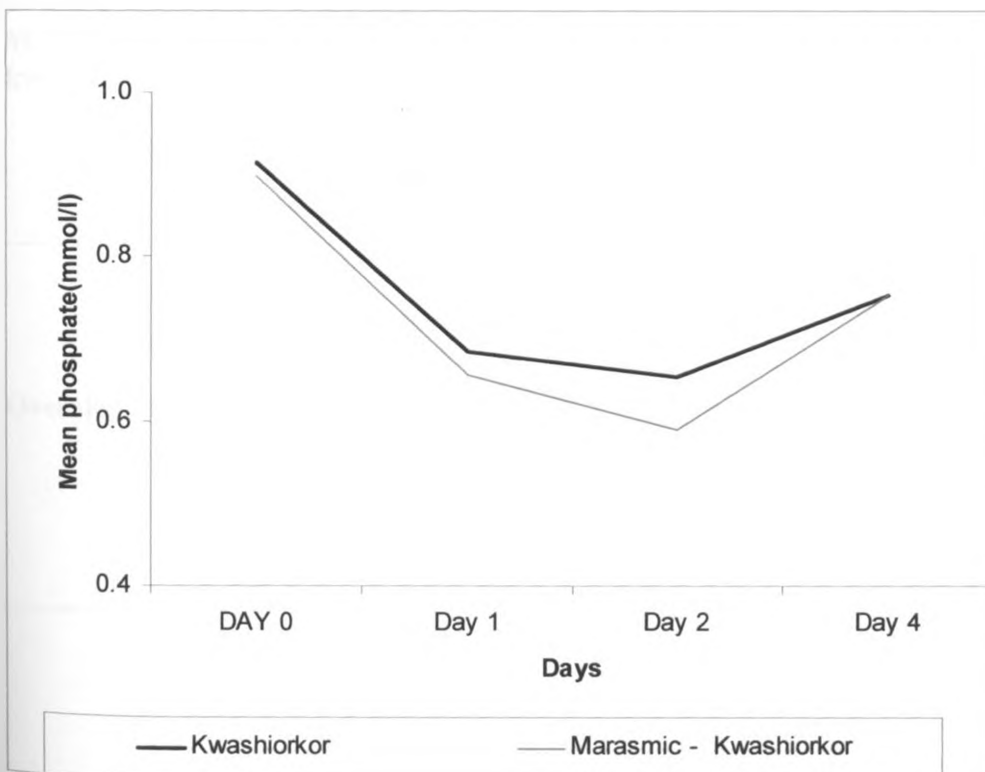


Figure 2 shows a similar pattern of decline in mean phosphate level from admission to day 2 with a rise noted on day 4 in both classes of malnutrition.

Table 6: Comparison of serum phosphate means at different time points in each class of malnutrition and overall.

Class	n	Day	Mean change (mmol/l)	95%CI	P-value
Kwashiorkor	107	0 & 1	0.23	0.18 to 0.28	<0.001
		0 & 2	0.28	0.21 to 0.36	<0.001
		1 & 2	0.06	0.01 to 0.12	0.025
		2 & 4	-0.14	-0.18 to -0.10	<0.001
		0 & 4	0.17	0.10 to 0.24	<0.001
Marasmic kwashiorkor	58	0 & 1	0.24	0.18 to 0.31	<0.001
		0 & 2	0.28	0.19 to 0.37	<0.001
		1 & 2	0.04	-0.02 to 0.09	0.162
		2 & 4	-0.14	-0.21 to -0.07	<0.001
		0 & 4	0.10	-0.02 to 0.21	0.096
Overall group	165	0 & 1	0.24	0.20 to 0.27	<0.001
		0 & 2	0.28	0.22 to 0.34	<0.001
		1 & 2	0.05	0.01 to 0.09	0.008
		2 & 4	-0.14	-0.17 to -0.10	<0.001
		0 & 4	0.14	0.08 to 0.20	<0.001

Paired t test was used to compare means at different time points in the whole study population and in each of the two classes of malnutrition. Mean serum phosphate level declined significantly by 0.24 mmol/l (95% CI 0.20 to 0.27) during the first 24 hours (P value < 0.001). Similar significant decline in mean serum phosphate level by 0.28 mmol/l (95% CI 0.22 to 0.34), was noted during the first 48 hours, P value <0.001. After the second day, mean serum phosphate level increased significantly by day 4 by 0.14mmol/l (95% CI -0.17 to -0.10), P value 0<0.001. The trends in phosphate levels were studied among kwashiorkor and marasmic kwashiorkor separately, and similar trends to those discussed were seen. However, there was no significant difference observed between days 1 and 2, P = 0.162 and between days 0 and 4, P = 0.096 in the marasmic kwashiorkor class (Table 6).

4.4 Association between hypophosphatemia and the various characteristics.

The relationship between severe hypophosphatemia on admission and the various demographic, clinical and biochemical characteristics was analysed. Chi-square test was used to determine whether there was any association.

Table 7: Association between severe hypophosphatemia and the various demographic, clinical and biochemical characteristics.

Characteristic		Severe levels n= 9	Normal and non-Severe Hypophosphatemia n= 156	P value
Malnutrition Class	Kwashiorkor	7 (78%)	100 (64%)	0.328
	Marasmic-kwashiorkor	2 (22%)	56 (36%)	
Sex	M	5 (56%)	90 (58%)	1.000
	F	4 (44%)	66 (42%)	
Age (months)	≤12	4 (44%)	62 (40%)	1.000
	>12	5 (56%)	94 (60%)	
Hydration status	No dehydration	4 (44%)	57 (37%)	0.727
	Dehydration	5 (56%)	99 (63%)	
Diarrhoea	Absent	5 (56%)	66 (42%)	0.501
	Present	4 (44%)	90 (58%)	
Presence of Infection	Yes	9 (100%)	125 (80%)	0.211
	No	0 (0%)	31 (20%)	
Presence of Dermatitis	Yes	6 (67%)	56 (36%)	0.082
	No	3 (33%)	100 (64%)	
IV Glucose given	Yes	1 (11%)	45 (29%)	0.447
	No	8 (89%)	111 (71%)	
Serum Albumin (g/l)	< 35	9 (100%)	124 (80%)	0.208
	≥35	0 (0%)	32 (20%)	
Serum Calcium (mmol/l)	< 2.2	7 (78%)	96 (62%)	0.486
	≥2.2	2 (22%)	60 (38%)	
Serum Magnesium (mmol/l)	< 0.60	7 (78%)	75 (48%)	0.099
	≥0.60	2 (22%)	81 (52%)	

There was no significant association between severe hypophosphatemia on admission and malnutrition class, sex, age, hydration status, diarrhoea, infection, dermatitis, iv glucose administration, albumin, calcium and magnesium as shown by the respective p values in table 7 above. However, there was some association noted between severe hypophosphatemia and dermatitis, $p = 0.082$; and with magnesium, $p = 0.099$ (Table7).

Children with dermatosis and low magnesium levels seem more likely to have severe levels of hypophosphatemia on admission.

4.5 Outcome following nutritional intervention.

A total of 21 children out of 165 (13%) died during the first one week following nutritional intervention. The mean phosphate level was calculated in the children who died and in those that survived on each day and Independent t test was used to compare them (Table 8).

Table 8: Comparison of mean serum phosphate levels during follow-up between those who died versus survivors.

Day	Died, n =21 Mean (mmol/l)	Alive, n =144 Mean (mmol/l)	95%CI	P value
Day 0	0.82	0.92	-0.24 - 0.39	0.153
Day 1	0.58	0.69	-0.03 - 0.07	0.227
Day 2	0.48	0.65	-0.37 - 0.04	0.097
Day 4	0.65	0.76	-0.37 - 0.15	0.351

Throughout the follow-up period, we noted that the mean serum phosphate level on any given day appeared lower among those who died than among survivors, although this difference was not statistically significant. However, a trend for statistical significance was noted on the 2nd day of treatment. $p=0.097$ (Table 8).

Figure 3: Trends of mean serum phosphate level during follow-up among those who died versus survivors.

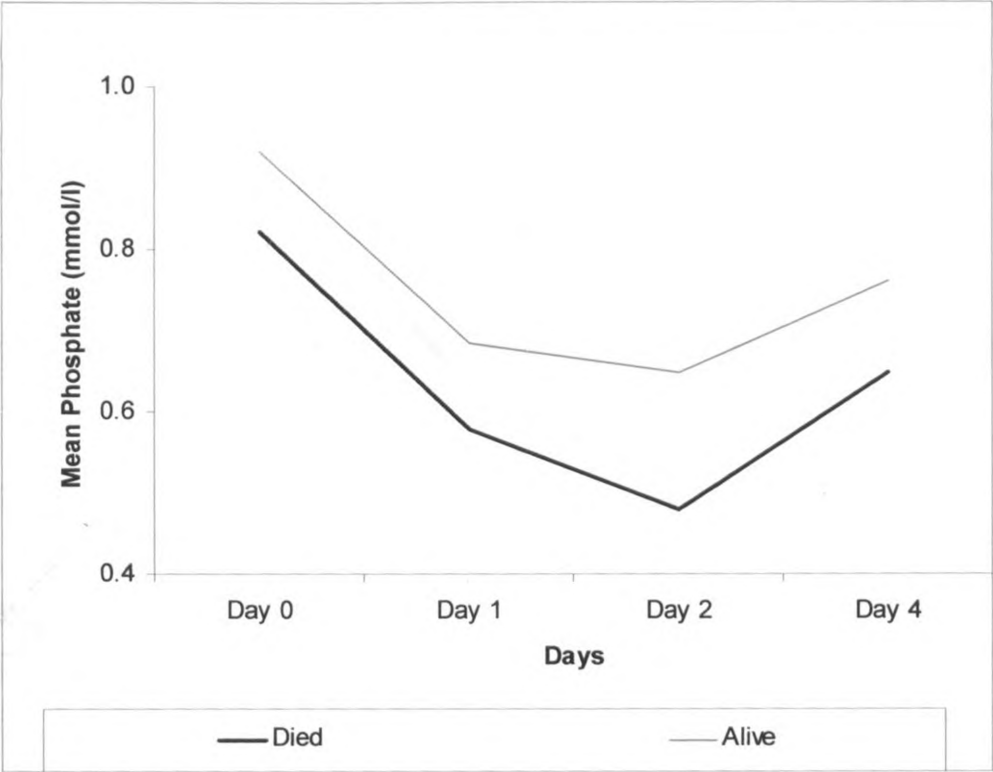


Figure 3 clearly shows that mean serum phosphate level was high for both groups on admission. Mean serum phosphate levels dropped significantly to their lowest on day 2 and a rise was noted on day 4. Of note was that, on all the days, the mean serum phosphate level for those who died was lower than for those who survived.

Table 9: Distribution of mortality during the 1st week in the hospital.

Day	0	1	2	3	4	5	6	Total
No. of deaths(%)	4(19)	3(14.5)	2(9.5)	4(19)	2(9.5)	2(9.5)	4(19)	21(100)

Table 9 above shows that there were at least 2 deaths each day during the 1st week of admission. It is observed that there are three peaks : on admission, on day 3 and on day 6 when most deaths occurred. The peak noted on day 3 comes a day after the mean serum phosphate nadir was observed (Table 5).

Table 10: Degrees of nadir serum phosphate level versus outcome by the end of 7 days in the hospital.

Degree of nadir phosphate		Out come			P value
		Died	Alive	Total	
Normal serum phosphate		0 (0%)	8 (100%)	8 (100%)	0.028
Hypophosphatemia	Mild	4 (8%)	49 (92%)	53 (100%)	
	Moderate	9 (14%)	57 (86%)	66 (100%)	
	Severe	8 (21%)	30 (79%)	38 (100%)	
Total		21 (13%)	144 (87%)	165 (100%)	

The nadir (lowest ever) serum phosphate level of each child was established and used to categorize children into either normal serum phosphate group or hypophosphatemia group. Children with hypophosphatemia were further classified by severity into mild, moderate and severe hypophosphatemia. None of the 8 children having normal serum phosphate died. Mortality rose with increasing severity of nadir hypophosphatemia from 0% among children with normal serum phosphate, to 8%, 14% and 21% among children with mild, moderate and severe hypophosphatemia respectively (Table 10).

The association between the hypophosphatemia and mortality was analysed using the chi-square test for linear trends. There was a significant association noted between mortality and increasing severity of hypophosphatemia, $p= 0.028$. Also noted was an increasing proportion of children who lived with decreasing severity of hypophosphatemia, with a similar p value. (Table 9 & Figure 4).

Figure 4: Association between severity of nadir hypophosphatemia and mortality.

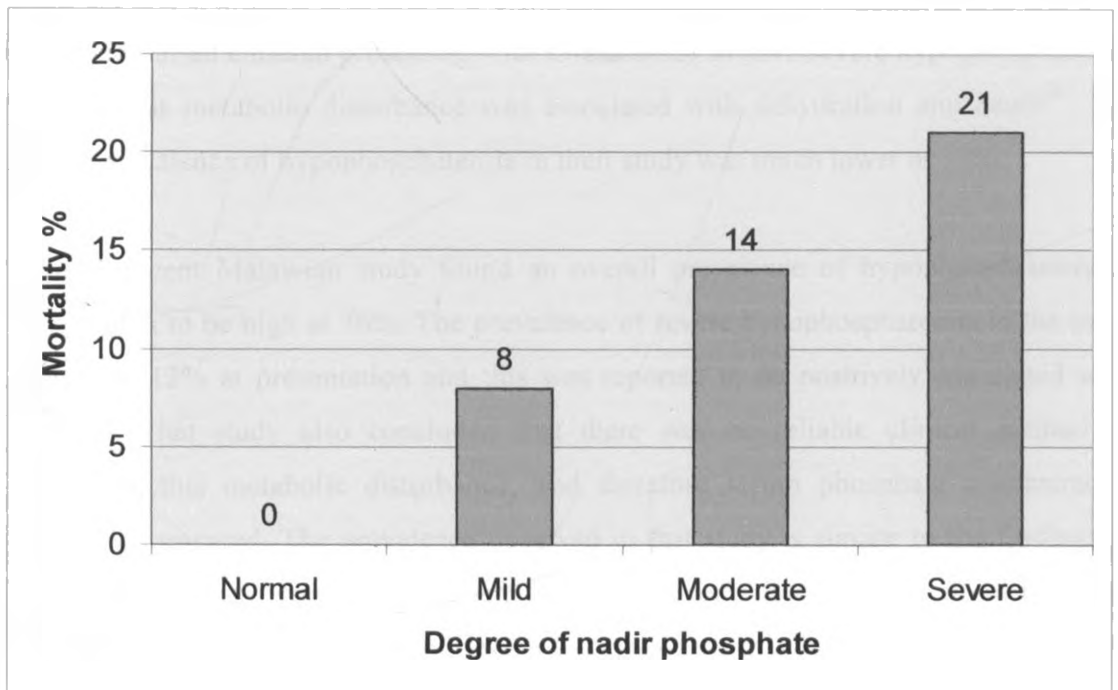


Figure 4 graphically illustrates increasing mortality with increasing severity of hypophosphatemia, from 0% among children with normal serum phosphate, to 8%, 14% and 21% among children with mild, moderate and severe hypophosphatemia respectively, $p = 0.028$ (Figure 4).

5.0 DISCUSSION

5.1 Prevalence of hypophosphatemia

This study demonstrates that hypophosphatemia is a frequent occurrence among children under five years with kwashiorkor and marasmic kwashiorkor admitted to the paediatric wards of KNH. An overall prevalence of hypophosphatemia of 86% at presentation and of severe hypophosphatemia of 6% was observed in our cohort. This is consistent with what has been found in other studies especially in Africa. Frieman et al in South Africa found 10% of all children presenting with kwashiorkor to have severe hypophosphatemia and that this metabolic disturbance was associated with dehydration and death²⁷. The overall prevalence of hypophosphatemia in their study was much lower at 57%.

A fairly recent Malawian study found an overall prevalence of hypophosphatemia at presentation to be high at 76%. The prevalence of severe hypophosphatemia in the same study was 12% at presentation and this was reported to be positively associated with death²⁸. That study also concluded that there was no reliable clinical method of identifying this metabolic disturbance: and therefore serum phosphate concentration should be measured. The prevalence observed in that study is similar to the findings in the current study. However, outside Africa, Waterlow et al in their study of 45 Jamaican children, did not observe cases of severe hypophosphatemia in kwashiorkor (including marasmic kwashiorkor) children³². Similarly, Kalra et al in India, did not observe cases of severe hypophosphatemia in kwashiorkor and marasmic kwashiorkor children³³.

Our findings therefore, suggest that in Sub-Saharan Africa, children with kwashiorkor appear to be especially susceptible to severe hypophosphatemia and that this complication may be related to the higher case fatality rates seen in Africa among these children²⁸. It has been thought that there may be environmental or genetic factors contributing to the occurrence of severe hypophosphatemia in kwashiorkor.

Similar high prevalences of hypophosphatemia were observed in two studies done in the paediatric intensive care units. Overall prevalences of over 50% were reported in both

studies¹⁷. Commonly associated with hypophosphatemia in these patients were malnutrition, refeeding syndrome, sepsis, trauma, and diuretic and steroid therapies. From these studies, a recommendation for early identification of this disorder and hence timely and adequate replacement therapy to avoid complications was made. The patients in the current study were all severely malnourished and being therapeutically refeed hence not surprising to find a high prevalence of hypophosphatemia both at presentation and during follow up.

Although there was no significant association between presence of infection and hypophosphatemia, a demonstration of an association has been reported in patients with early sepsis, pneumonia or other bacterial infections^{18,19}. These conditions are associated with hyperventilation and hence alkalosis which is thought to promote intracellular shifts of phosphate⁹. Antachopoulos et al demonstrated that hypophosphatemia is a relatively mild, frequent and transient phenomenon in paediatric patients with acute infectious disease³⁴. A large proportion, 134 (81%) of patients in the current study was reported to have an infectious disease. This therefore, can further explain the high prevalence of hypophosphatemia in our cohort.

We speculate that the prevalence of severe hypophosphatemia of 6% might not portray the true picture of the magnitude of severe phosphorus deficiency in this cohort. This is because during starvation, there is catabolic release of phosphate from intracellular stores so that the normal phosphate levels can be maintained. Released phosphate is subsequently lost in the urine and therefore significant total body phosphate depletion can occur despite normal serum phosphate levels¹⁶. Severely malnourished children most often have had a long-term relatively low phosphate intake which predisposes them to significant total body phosphate depletion^{9,17}.

The hypophosphatemia on admission was not significantly associated with malnutrition class, sex, age, hydration status, diarrhoea, infection, dermatosis, iv glucose administration, serum albumin, calcium and magnesium concentrations. Manary et al²⁸ found similar observations except in dehydration and dermatosis where they found a

significant association. A similar, significant association with dehydration was observed by Frieman et al²⁷. There is no clear explanation to these findings, however, Knochel et al in their review article reports an increase in serum phosphate during states of dehydration and one would therefore expect a cancelling out effect to occur with the loss accruing from diarrhoea as observed by Golden et al³².

Phosphate loss has been reported to occur from open lesions and therefore, it is not surprising to find an association between hypophosphatemia and dermatosis as reported by Manary et al²⁸. In our cohort, a trend for association with dermatosis was observed. The current study also found a trend for association with hypomagnesaemia. It has been demonstrated that magnesium deficiency leads to phosphaturia and subsequently hypophosphatemia⁹. It is therefore, not surprising to find an association between hypophosphatemia and hypomagnesaemia in this study⁹.

In this cohort, the prevalence of hypophosphatemia at admission was high at 86%, with 54%, 26% and 6% having mild, moderate and severe levels respectively. With such a high prevalence of severe hypophosphatemia among these children, and there being no reliable clinical method for identification of this metabolic disturbance, serum phosphate should at least be measured at admission²⁸.

5.2 Trends of serum phosphorus in the first 5 days.

Refeeding syndrome is defined as the occurrence of severe fluid and electrolytes shifts (especially, but not exclusively, of phosphate) and their associated complications in malnourished patients undergoing enteral/parenteral refeeding^{7,35}. Refeeding syndrome is one of the few diagnoses associated with profound hypophosphatemia due to intracellular shifts of phosphorus^{9,24}. It is known that malnourished children are depleted of phosphorus due to renal loss and inadequate intake during starvation. During refeeding, there is a sudden introduction of carbohydrate which stimulates insulin release. Insulin subsequently increases cellular uptake of glucose, phosphate and water into cells and this results in a severe hypophosphatemia, a central component of the refeeding

syndrome. Up to 86% of our patients already had hypophosphatemia on admission and hence it is not surprising to see a rise in severe forms of hypophosphatemia with nutritional repletion.

Worldwide, there are very few studies on refeeding syndrome in children and especially so in kwashiorkor during enteral feeding. Afzal et al report 27 children (<18 years) that developed refeeding syndrome characterized by a fall in phosphate after enteral feeding with high calorie feeds. In general, these children were malnourished (weight range 45-75% of ideal weight for height) with seven of them having kwashiorkor⁷. The cohort in our study, comprised severely malnourished children with a W/A below 80% and were similarly undergoing nutritional intervention with a high calorie diet. And therefore, the development of refeeding hypophosphatemia is not surprising.

This study demonstrated a relatively higher mean serum phosphate of 0.91mmol/l on admission. Only 6% of the patients were found to have severe hypophosphatemia at admission. On follow up, phosphate levels significantly dropped with a simultaneous rise in percentage of severe hypophosphatemia, peaking after 2 days. Manary et al observed a similar trend where 12% of patients developed severe hypophosphatemia within 48 hours of nutritional intervention²⁸. Their study however, did not follow up patients beyond 48 hours and therefore, trends of serum phosphate beyond this time is not known. Similar trends have also been observed in patients with severe chronic alcoholism, generally but not always in association with poor nutrition⁹. After hospitalization, the alcoholics develop a severe hypophosphatemia that reaches its nadir on the second to fourth day of hospitalization as during the admission, administration of large amounts of carbohydrates is done. From our cohort, 22% of the patients attained severe levels as early as 48 hours and a rise in mean phosphate level is observed on day 4.

Patients who are at the greatest risk of developing refeeding syndrome include those with kwashiorkor, marasmus, anorexia nervosa, chronic malnutrition, chronic alcoholism and prolonged fasting^{4,25}. Mezoff et al report a hypophosphatemia prevalence of 56% in malnourished children⁴. This prevalence is much lower than the prevalence in our study.

The symptoms of refeeding syndrome are largely secondary to hypophosphatemia and include cardiac, neuromuscular and haematologic dysfunction. Laboratory indicators of refeeding syndrome include a rapid decrease in serum phosphate, potassium, magnesium and sodium, as well as fluid intolerance³⁷. The current study did not endeavour to look at the symptomatology. However, serial serum phosphate was measured in the first four days post admission and a sharp decline in serum phosphate levels was observed within two days.

Afzal et al described an adolescent girl with Crohn's disease who developed refeeding hypophosphatemia after starting polymeric enteral nutrition⁷. Serial phosphate levels were done on selected days up to day twelve and a nadir serum phosphate of 0.23 mmol/l was attained on day 5 after admission. In our cohort, serial phosphate levels were only determined up to day 4 due to financial constraints. Considering the above case report, and the fact that some of our children were still experiencing a drop in their serum phosphate level by day 4, we think that nadir serum phosphate in some patients could be occurring even much later than day 4 of nutritional intervention. It would be of value therefore, to consider a much longer monitoring period of serum phosphate levels in these children.

Marik et al studied a heterogenous group of 62 intensive care unit adult patients who were undernourished and had undergone a period of starvation lasting more than 48 hours³⁶. They found 21(34%) of their patients to have developed refeeding hypophosphatemia with a nadir serum phosphate attained after about 2 days. They also demonstrated a longer period of mechanical ventilation and hospital stay for patients who had developed hypophosphatemia. In their study, the finding of a nadir serum phosphate after 2 days resembles the findings in our cohort and also demonstrates that refeeding hypophosphatemia can accompany fairly short periods of starvation due to the intracellular phosphate shifts.

Similar trends to those observed in our cohort have also been observed in adult studies as well. Weinsier et al reported two adult cases with severe malnutrition that developed severe hypophosphatemia within 48 hours of total parenteral nutrition²⁴. Their serum

phosphate levels similarly showed an upward trend on day 4. Both patients died soon afterwards from complications of the refeeding syndrome. It is believed that refeeding hypophosphatemia significantly contributed to their deaths due to the close temporal relationship between declining serum phosphate level and their acute cardiac decompensation.

This study demonstrates an increase in prevalence of hypophosphatemia during nutritional intervention, from 86% at baseline to 90% and 93% at day 1 and 2 respectively, and was still high at 89% on day 4. Severe hypophosphatemia prevalence similarly rose to 18% and 22% on day 1 and 2 respectively and dropped to 11% on day 4. Mean serum phosphate levels took a downward trend with a nadir on day 2 and a rise noted on day four. Intravenous phosphorus may be beneficial for severe hypophosphatemia complicating kwashiorkor, but there is little published experience. Intravenous phosphorus is, however, given routinely as infusion over 6 hours in treating severe hypophosphatemia associated with critical illness in intensive care units.^{4, 17, 29}

5.3 Outcome during the first week of nutritional intervention.

A total of 21 of 165 (13%) patients died in the first week while getting nutritional therapy. From this cohort, it was demonstrated that there is an increasing mortality with increasing severity of nadir serum phosphate level. A similar finding has been observed in other studies elsewhere^{24, 27, 28}. However, the mortality in this cohort may be slightly lower and this may be attributable to the erratic and inadequate supply of feed administered to these children in this setting. This scenario of sub optimal intake of calories tends to be inadvertently protective against the effects of the refeeding syndrome. Therefore, in most instances, refeeding syndrome is treated by cautious progressive nutrition achieved by a reduction in volume and caloric density of the feeds^{7, 21, 22, 38}.

Manary et al found 5 of 8 (63%) of patients who developed severe hypophosphatemia during refeeding to have died as compared to 22% who died among those without severe hypophosphatemia, P value <0.02²⁸. In our study, 21% (8 of 38) of patients with severe

hypophosphatemia died. This slightly lower figure may be attributable to the sub optimal feeds as mentioned earlier. Frieman et al found 10% of children presenting with kwashiorkor in South Africa to have severe hypophosphatemia that was associated with death²⁷. Weinsier et al report two adult cases with severe malnutrition that developed severe hypophosphatemia within 48 hours of total parenteral nutrition²⁴. Both patients died afterwards and their deaths were thought to be due to acute metabolic imbalances (mainly hypophosphatemia) and the following multiple organ dysfunction.

Hypophosphatemia has been reported to be responsible for numerous deleterious consequences; especially in its severe form, it hampers clinical recovery of the patient and is associated with high morbidity and mortality³⁹. Untreated, hypophosphatemia leads to depletion of phosphorylated compounds such as adenosine triphosphate (ATP) and 2,3-diphosphoglycerate (2,3-DPG) and might result in cardiac, neuromuscular, haematological and respiratory compromise⁷. These consequences of hypophosphatemia may explain the fact that deaths were observed in all the hypophosphatemia categories of our study. In our cohort, the largest proportion of deaths, 9 of 21 (43%) is observed in the moderate category as compared to 8 of 21 (38%) observed in the severe category (Table 10). This could be explained by the fact that a larger number of patients, 66(40%) were found in the moderate category as compared to 38(23%) in the severe category. However, a larger proportion, 21%, of children died in the severe category as compared to 14% in the moderate category.

In the current study, it was demonstrated that a modest proportion of 19% of the deaths occurred a day after the mean nadir serum phosphate. The deaths on admission could be attributable to the initial complications of malnutrition observed on admission such as hypoglycaemia, hypothermia, and dehydration^{6,8}. The rest of the mortalities are distributed throughout the week(Table 9). There are no similarly designed studies to compare with our findings. However, Manary et al²⁸ attributed 5 of 8 (63%) of mortalities to hypophosphatemia in the first 48 hours of admission. They only followed up their cohort to 48 hours after admission. Other reports which comprise mainly case studies, have reported mortality to occur even later than the first week^{7,24}. This observation is

mainly seen in situations where facilities like the intensive care units exist for purposes of mechanical ventilation.

The findings from our cohort clearly demonstrates a positive association between severity of hypophosphatemia and mortality, with an observed mortality of 0% among children with normal phosphate and 8%, 14% and 21% among children with mild , moderate and severe hypophosphatemia. This underscores the need for phosphate replacement in children with kwashiorkor. However, since there is paucity of data on this subject, a study should be carried out to assess the efficacy and safety of phosphorus supplementation in kwashiorkor and marasmic kwashiorkor children.

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5.4: Study limitations.

Although we explored the demographic, clinical and laboratory correlates of hypophosphatemia, the study was not designed to answer that question and therefore was under-powered to demonstrate clearly the presence or absence of associations.

Due to reasons of logistics, the amount and type of feed prescribed could not be measured during the study period. The contribution to mortality by other electrolytes other than calcium and magnesium was not assessed due to financial constraints, and therefore may act as confounders. Other confounders that may have contributed to mortality include hypoglycaemia, hypothermia, dehydration and infections. Follow-up of patients to discharge was not done as only the first week was considered. Therefore, full outcome during the admission for every child could not be observed.

6.0 CONCLUSIONS AND RECOMMENDATIONS.

6.1 Conclusions

1. Prevalence of hypophosphatemia was high among children with kwashiorkor and marasmic kwashiorkor: 86% on admission, with 54%, 26% and 6% of children exhibiting mild, moderate and severe levels respectively.
2. Prevalence of hypophosphatemia increased during nutritional intervention to 91% and 93% on day 1 and 2 respectively, and still remained high (89%) on day 4. Severe hypophosphatemia rose to 18% and 22% on day 1 and 2 respectively and dropped to 11% on day 4.
3. Mean serum phosphate level fell significantly during nutritional intervention from 0.91mmol/l on admission to 0.63 mmol/l on day 2, P-value <0.001; thereafter the level rose to 0.75mmol/l on day 4 ($p = <0.001$).
4. Although this study was not adequately designed to measure outcome, there was an observed positive association between severity of nadir hypophosphatemia and mortality; with an observed mortality of 0% among children with normal phosphate and 8%, 14% and 21% among children with mild, moderate and severe hypophosphatemia ($p = 0.028$).

6.2 Recommendations

1. Given the high prevalence of hypophosphatemia, there is a need for routine measurement of serum phosphate in all kwashiorkor and marasmic kwashiorkor children presenting at KNH. A repeat test on the 2nd post-admission day is indicated.
2. There is a need for further research to evaluate the efficacy of the gradual introduction and progressive increase of calories on the reduction of hypophosphatemia, and subsequent outcome in children with kwashiorkor and marasmic kwashiorkor presenting at KNH.
3. There is a need for further research to assess the efficacy and safety of phosphorus supplementation in children with kwashiorkor and marasmic kwashiorkor presenting at KNH.

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APPENDICES

APPENDIX I

CONSENT FORM FOR STUDY PARTICIPATION.

TITLE: To assess the magnitude of hypophosphatemia in children under five years of age, with Kwashiorkor and marasmic kwashiorkor, before and after nutritional intervention at KNH.

Study No. _____

Hospital No. _____

<u>Investigators</u>	<u>Role</u>
Dr David Kimutai	Researcher
Dr R. Kamenwa	Supervisor
Dr E. Obimbo	Supervisor
Dr F. Murila	Supervisor

Contact Person

Dr David Kimutai; PO Box 74860-00200 NAIROBI

Telephone 0722-975048

Investigators' Statement

We are asking you to be in a research study. The purpose of this consent form is to give you the information you will need to help you decide whether or not to be in this study.

Introduction

Phosphorus is an intracellular ion involved in the cellular structure and function. It is important in the metabolic and energy pathways of the cell. Studies have shown that it becomes less in malnutrition and it tends to go lower as soon as proper feeding is initiated. This may possibly worsen the patient's condition. The research aims at determining the level of phosphorus in children with kwashiorkor and marasmic kwashiorkor on admission, and subsequently in the next five days after therapeutic feeding is started. This will help us to see the magnitude and how we can prevent or treat this condition if indeed it is proven to occur.

Procedures

A history will be taken from you concerning your child's illness. The child will subsequently be examined fully and clinical findings noted. A blood sample of 2 millilitres (mls) will be taken from a vein and taken to the laboratory to determine the

levels of phosphorus, calcium albumin and magnesium. On days 1,2 and 4, a further 2 mls each of blood will drawn to determine serial level of serum phosphorus.

Voluntariness

The study will be fully voluntary. One is free to refuse to participate or withdraw from the study. Refusal to participate will not compromise the child's care in the hospital in any way.

Benefits of the study

Your child will be fully examined and a diagnosis made. Any illnesses found will be addressed according to the standard hospital protocol. Any advice will be given as needed.

The study will help the hospital to formulate guidelines on the management of low phosphate levels.

Risks of the study

During the study, we will take your time and ask you personal questions. We will also draw several blood samples from your child.

Confidentiality

All the information received will be held in the strictest confidence and information to identify you will not be released to any person or forum without your permission. Nothing will be published or discussed in public that can identify you.

Do you have any questions? _____

Do you agree to participate? Yes _____ No _____

Signature of investigator _____ Name of investigator _____

Date _____

Mother/Guardian's statement

The study described above has been explained to me. I agree to participate in the study. I have had a chance to ask questions; and I have been assured that if I have future questions about the research or my rights as a subject, I can ask the investigator listed above.

I understand that I am free to withdraw from the study at any time.

Signature _____ Name _____

Date _____

Signature of witness

If thumbprint used _____ Name _____ Date _____

APPENDIX II

DATA FORM

Name: _____ Research Number _____

Age (mo): _____ Sex: _____ Wgt (kgs) _____

% of expected _____

DOA: _____ Ward: _____ Diagnosis: 1. _____

2. _____

IP Number _____ 3. _____

Hydration status

No dehydration _____

Some dehydration _____

Severe dehydration _____

Duration of diarrhoea if any

Nil _____

Acute _____

Chronic _____

Infection: Yes _____

No _____

Dermatosis: Present _____

Absent _____

Intravenous glucose: Yes _____

No _____

Serum Pi (mmol/l)

Degree

Admission(Day 0) _____

Day 1 _____

Day 2 _____

Day 4 _____

Serum albumin on admission (g/l) _____

Serum calcium on admission (mmol/l) _____

Serum magnesium on admission (mmol/l) _____

Outcome (Day 7): Alive _____

Died _____ Day post adm. _____

APPENDIX III

DEFINITION OF TERMINOLOGY

1. Table 11: Wellcome classification of malnutrition⁷.

Weight -for-age (% of standard)	Oedema absent	Oedema present
60-80%	<i>underweight</i>	<i>Kwashiorkor</i>
<60%	<i>Marasmus</i>	<i>Marasmic kwashiorkor</i>

2. Diarrhoea - >3 watery stools in 24 hours⁷

Acute diarrhoea : < 2weeks duration.

Chronic diarrhoea : > 2weeks duration

3. Dehydration⁵

<u>Observation</u>	<u>A</u>	<u>B</u>	<u>C</u>
a) Condition	well, alert	restless, irritable	lethargic.
Eyes	normal	sunken	very sunken, dry
Tears	present	absent	absent
Mouth/tongue	moist	dry	very dry
Thirst	drinks normally	drinks eagerly	poorly/ unable
b) Skin pinch	goes back quickly	goes slowly	goes very slowly
Diagnosis	No dehydration	Some dehydration	Severe dehydration

4. Phosphate levels in children^{9,12,32}

Normal range : 1.20 – 2.30 mmol/l

Hypophosphatemia: <1.20mmol/l

5. Hypophosphatemia^{9,12,32}

Mild : 0.8 - 1.19mmol/l

Moderate : 0.33- 0.79mmol/l

Severe : <0.33mmol/l

6. Albumin reference range³² : 39 – 50 g/l

7. Calcium reference range³² : 2.2 – 2.7 mmol. l

8. Magnesium reference range³² : 0.60 – 0.95mmol/l

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Ref: KNH-ERC/01/2641

Date: 15th April 2005

Dr. David Kimutai
Department of Paediatrics
Faculty of Medicine
University of Nairobi.

Dear Dr. Kimutai

**RESEARCH PROPOSAL : "TO ASSESS THE MAGNITUDE OF HYPOPHOSPHATEMIA
IN CHILDREN UNDER FIVE YEARS WITH KWASHIORKOR AND MARASMIC
KWASHIORKOR BEFORE AND AFTER NUTRITIONAL INTERVENTION AT
KENYATTA NATIONAL HOSPITAL" (P156/12/2004)**

This is to inform you that Kenyatta National Hospital Ethics and Research Committee has reviewed and **approved** revised version of your above cited research proposal for the period 15th April 2005 to 14th April 2006. You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given.

On behalf of the Committee, I wish you fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of database that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely,

PROF. A. N. GUANTAI
SECRETARY – KNH-ERC

Cc: Prof. K. M Bhatt, Chairperson, and KNH-ERC
The Deputy Director (C/S), KNH
The Dean, Faculty of Medicine, UON
The Chairman, Dept. of Paediatrics, UON
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