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Serum Phosphorus Level in ALL Children - Case Control Study

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Abstract

Background – Acute lymphoblastic leukemia (ALL) is the most prevalent childhood leukemia and metabolic changes with electrolyte abnormalities are commonly seen during the course of the disease and therapy. Phosphorus changes in the serum have been reported in children with ALL, especially during the occurrence of TLS and metabolic changes induced by chemotherapy.

Objective: To compare the serum phosphorus levels of ALL children with healthy controls and to determine the association of the serum phosphorus level with age, gender, FAB classification, chemotherapy cycles and disease duration.

Design: 50 children with ALL (cases) and 30 healthy children (controls) aged 1-16 years were included in this case control study. Serum phosphorus was determined and compared among groups. To assess associations with demographic and clinical parameters, such as gender, age groups, FAB classification (L1, L2, L3), number of chemotherapy cycles and disease duration, statistical analysis was conducted.

Results: The study included 35 boys (70%) and 15 girls (30%). FAB classification showed L1 in 43 patients (86%), L2 in 1 patient (2%), and L3 in 6 patients (12%). Mean serum phosphorus was 4.4±0.8 mg/dL in cases versus 4.1±0.6 mg/dL in controls (P=0.109). No statistically significant differences were found by gender (boys 4.47±0.84 vs girls 4.15±0.70 mg/dL, P=0.729), age groups (1-8 years 4.56±0.70 vs 9-16 years 4.19±0.89 mg/dL, P=0.113), FAB type (L1 4.29±0.79, L2 4.20, L3 5.02±0.80 mg/dL, P=0.115), chemotherapy cycles (<10 cycles 4.59±0.73 vs ≥10 cycles 4.27±0.83 mg/dL, P=0.191), or disease duration (P=0.083).

Conclusions: Mean serum phosphorus levels were slightly higher in children with ALL than in controls but the difference was not statistically significant. The lack of clinical associations indicates that, in stable ALL patients, outside of the period of acute tumor lysis, there is relative preservation of phosphorus homeostasis. But it is important to keep an eye out during certain time of a person's life, such as when they are undergoing chemotherapy and diagnosis.

Keywords: ALL; phosphorus; Leukaemia; Paediatric and haemostasis

1. Introduction

Acute lymphoblastic leukemia (ALL) is the most frequent form of cancer in children, comprising about 25-30% of all forms of childhood cancer and 75-80% of all leukemias in children. Epidemiological studies have been conducted worldwide and there are significant geographical and population differences in the incidence with annual incidence rates ranging from 2 to 5 per 100,000 children [1] [2]. The disease has a typical age-specific distribution with most cases occurring between 2 and 5 years of age [2] and there is a slight male predominance, with a male to female ratio of 1.2:1

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to 1.4:1 [2]. The last decade, epidemiological studies have identified time trends with stable or slightly rising incidence in numerous regions over the past 30 years, with the underlying causes of such trends not always fully understood [3].

Over the last few decades, the prognosis of paediatric ALL has improved significantly and today, modern treatment protocols provide 5-year event-free survival rates of >85-90% in developed countries where specialized paediatric (hemato-oncology) centers are available [4]. The progress made in the field is remarkable, in terms of advances in risk stratification, optimization of multi-agent chemotherapy regimens, better supportive care and management of treatment-related complications. However, the treatment regimens of today, like ALL-IC BFM 2002 and its updates, have proven to yield very good results in varying populations, with clear differences between the results achieved in low and middle income countries as compared to high income countries [5] [6]. Treatment at specialized paediatric hemato-oncology centers has been shown to greatly influence survival rates over that of non-specialized centers, thus highlighting the importance of centralised treatment for a complex disease [4]. Recent protocols have also optimized risk stratification - some favorable cytogenetic subgroups (e.g., ETV6::RUNX1 fusion-positive ALL) have been shown to have excellent outcome with less intensive therapy with others (e.g., chromosomal abnormalities, persistence of minimal residual disease) being high-risk for which intensification of therapy should be considered [7, 8].

ALL can be classified into three morphological groups, L1, L2 and L3, using the French-American-British (FAB) classification system, which was developed in the 1970s and then refined over the past few decades. The L1 subtype is the most common morphological type with small, uniform lymphoblasts whose nuclear contours are regular and their cytoplasm is scanty, accounting for about 80-85% of ALL in children. The L2 subtype is characterised by larger and more variable lymphoblasts with irregular nuclear outlines and a more copious cytoplasm, and accounts for about 10-15% of the cases. The L3 subtype occurs only 1-2% of cases of pediatric ALL, and is the most mature form of B-cell leukemia (Burkitt leukemia), characterized by large homogeneous cells with prominent cytoplasmic vacuolation and deeply basophilic cytoplasm [9]. Today, the FAB classification has been largely replaced by immunophenotypic and molecular classification, but it is still relevant to recognize the heterogeneity of the disease, and it has historical relevance in the development of protocols. L3 is an important subtype because of its unique biological properties, its aggressive clinical course, and its association with unique complications of therapy, such as an especially high risk for tumor lysis syndrome [9, 10]. Metabolic problems are a major difficulty in the care of ALL in children; they have been associated with the disease state and the high dose chemotherapy used to treat ALL. One of the most severe metabolic emergencies in paediatric oncology is tumour lysis syndrome (TLS), characterized by massive release of intracellular metabolites into the circulation as a result of rapid death of malignant cells that results in hyperuricemia, hyperkalemia, hyperphosphatemia and secondary hypocalcemia. The prevalence of TLS in pediatrics ALL is also highly variable based on the definition of TLS, risk factors and prophylactic strategies, ranging from 3% to 42% in different series [11]. The clinical risk factors for the development of TLS have been identified by clinical studies, such as high white blood cell (WBC) count at diagnosis (more than 50,000–100,000/μL), bulky extramedullary disease, elevated lactate dehydrogenase (LDH) levels, pre-existing renal impairment, and particular disease subtypes including mature B-cell leukemia (FAB L3) [11, 12]. Hyperphosphatemia may be quite significant and life-threatening, with serum phosphorus levels often exceeding 10-15 mg/dL, and can lead to acute kidney injury due to calcium-phosphate precipitation in renal tubules [12]. In contemporary management, the emphasis is on risk stratification, vigorous hydration, proactive management of hypouricaemia (allopurinol or rasburicase) and close monitoring of electrolytes and renal function during the first few days of therapy [11,12].

In addition to the immediate electrolyte and metabolic abnormalities associated with TLS, children with ALL might have different abnormalities at other times during their illness and treatment. Phosphorus, when present in the blood stream can be found as a part of the serum and has a crucial role in many physiological processes such as bone mineralisation, energy metabolism via ATP synthesis, cellular signaling, membrane structure and acid-base balance. Serum phosphate levels vary by age reflecting the need for growth and bone development, and are 4.0-7.0 mg/dL in infants and young children, 3.5-6.0 mg/dL in school-age children and 3.0-5.5 mg/dL in adolescents [13]. The mechanisms responsible for the maintenance of phosphorus homeostasis are complex and involve intestinal absorption, renal excretion, and bone metabolism, all regulated by a number of hormones, most notably parathyroid hormone (PTH), 1,25-dihydroxyvitamin D, and fibroblast growth factor 23 (FGF23). Many mechanisms for the disruption in phosphorus metabolism associated with malignancy in pediatrics exist such as tumor cell lysis, chemotherapy-induced cellular injury, changes in renal functions, nutritional changes, and hormonal changes [13].

Children with ALL often have problems with the way their bones break down calcium and phosphates, either at the time of diagnosis or while undergoing treatment. All patients with paediatric ALL have been shown to have decreased bone mineral density, disturbed calcium and phosphorous metabolism and disturbances of bone regulating hormones [13]. These abnormalities can be caused by the disease process itself, such as leukemic infiltration of bone marrow or by treatment-related effects, such as corticosteroid treatment, exposure to methotrexate, and decreased physical activity

during periods of intensive treatment. Bone mineral density deficits can last for several years after completion of therapy with some studies indicating a greater risk of fractures and long term skeletal complications [13]. Another recent study has also demonstrated the role of vitamin D status and calcium-phosphorus balance in children with ALL and some correlations have been proposed with treatment response [15]. One of the genetically most prevalent subtypes of ALL in children, the ETV6::RUNX1 fusion-positive ALL has been specifically investigated on this topic with results indicating that this subgroup may present with different patterns of bone mineral metabolism disturbances during and after treatment [16]. Metabolic monitoring is known to be important in paediatric ALL, but there is limited understanding of the distribution of serum phosphorus concentrations when outside of the acute TLS context. Hyperphosphatemia in TLS is well described and much studied but little attention has been paid to the understanding of phosphorus homeostasis in stable ALL patients in maintenance therapy or long term survivors of ALL. The phosphorus level has been suggested as being within normal limits for most stable ALL patients, or minimal elevations or changes in phosphorus metabolism that might not be clinically identified as TLS but may be physiologically significant [11, 20]. The pattern of serum phosphorus in various clinical settings, disease subtype and treatment phases is significant and helps guide targeted monitoring and identify patients that could benefit from closer metabolic monitoring.

There is a need for systematic investigation of the relationship between serum phosphorus level and some clinical variables in the pediatric ALL cases. However, there are well-known differences in phosphorus homeostasis between age groups in healthy children, with lower children having higher levels of serum phosphorous to facilitate fast bone growth and development [13]. It is important to know if these age-related patterns are present in children with ALL and whether the disease or treatment of ALL affects these relationships. Likewise, there are few reports of potential sex differences in the metabolism of pediatric ALL patients, although some epidemiological evidence suggests that male patients may have a different metabolic profile than female patients [2]. Since the FAB subtypes have been shown to be linked with the risk of TLS, the correlation between the FAB subtypes and the levels of phosphorus is of special interest, but it is not evident whether there are more subtle differences between FAB subtypes in stable patients [9].

The effect of treatment intensity and length on phosphorus homeostasis in children with ALL should also be studied. Treatment for ALL consists of several different phases: remission induction, consolidation, and long-term maintenance therapy, and the total amount of chemotherapy exposure depends on the risk classification. Some of the chemotherapy regimens can affect phosphorus metabolism either directly or indirectly via their effects on renal function, bone marrow recovery, nutrition status and metabolic homeostasis [17]. There have been some studies that indicate repetitive chemotherapy can cause cumulative effects on the function of the kidneys' tubules and could have an impact on the handling of phosphorus [20]. Moreover, the duration of the disease itself could be a factor, as the longer the period after diagnosis, the more likely the metabolic homeostasis might be restored or, on the other hand, cumulative treatment-related effects on the regulation of phosphorus. Knowledge of the mechanisms of phosphorus homeostasis in paediatric ALL is not just relevant to the management of TLS, but has clinical implications. Even slight changes within the normal range of phosgene oxime levels could be significant for bone health, energy metabolism and general physiological function during the intensive treatment phase and beyond. Additionally, the clinical predictors of phosphorus levels could be used to develop risk-stratified monitoring strategies, such as more frequent monitoring of high-risk patients and less frequent monitoring of low-risk patients, potentially reducing the number of unnecessary tests for low-risk patients [9]. Given the recent advances in molecular biology of ALL, which identified multiple molecular subtypes with different biological features and response to therapy, it is plausible to ask whether the various molecular subtypes could also have different metabolic profiles [8, 16]. Recurrence of ALL is a further challenge in management as high treatment-related mortality and requirement for intensive salvage regimens with potential for increased metabolic risks have been shown [18, 19]. Baseline metabolic parameters such as phosphorous in the relapsed setting and how this differs from newly diagnosed patients may guide supportive care strategies. With the introduction of novel therapies such as chimeric antigen receptor (CAR) T-cell therapy, which has revolutionized treatment of relapsed/refractory ALL, baseline metabolic assessment is becoming more important as these treatments come with their own metabolic complications, such as cytokine release syndrome and tumor lysis syndrome [7, 8]. This is a case-control study, as there is a lack of current knowledge about the levels of serum phosphorus in children with ALL outside the context of acute TLS, and because the understanding of the role of phosphorus homeostasis may be important for distinct subgroups of patients with ALL and in different phases of treatment. The main aim was to measure the serum phosphorus level in ALL and healthy children. Secondary objectives were to investigate the relationship of serum phosphorus concentrations with important clinical parameters such as age, sex, FAB morphological classification, number of chemotherapy cycles administered and duration of the disease. We hypothesized that ALL children may exhibit an altered phosphorus homeostasis relative to healthy controls and specific clinical subgroups may exhibit different patterns of phosphorous levels [20]. The results of this study may help increase knowledge of the metabolic homeostasis of paediatric ALL and guide evidence-based metabolic monitoring strategies in children.

2. Materials and Methods

2.1. Study Design and Setting

The study protocol was reviewed and approved by the institutional ethics committee and informed consent was obtained from parents/legal guardians of all participants and assent was obtained when appropriate from children according to their age and developmental status.

2.2. Study Population

Patients: 50 children with a diagnosis of acute lymphoblastic leukemia (ALL) based on the standard morphological, immunophenotypic and molecular criteria. Exclusion criteria for cases were: (1) bone marrow examination revealing <25% lymphoblasts; (2) age <1 year or >16 years when the study was conducted; (3) treatment not in accordance with normal ALL treatment; and (4) evidence of active tumor lysis syndrome at the time of blood sampling. The exclusion criteria were: (1) acute tumour lysis syndrome or acute metabolic crisis at the time of sampling, (2) current acute illness or infection, (3) known pre-existing renal disease, (4) known disorder of calcium or phosphorus metabolism and (5) refusal of consent.

Thirty healthy children (age 1-16) years were recruited as controls. The children were chosen from a group of children attending the hospital as part of a regular health checkup, for minor procedures, or to accompany family members to the hospital; and were identified as healthy by history, physical examination, and lack of acute or chronic illness. The exclusion criteria for controls were: (1) any acute or chronic disease; (2) use of drugs that may influence phosphorus metabolism; (3) known renal disease; (4) known disease of calcium or phosphorus metabolism and (5) refusal of consent.

2.3. Data Collection

Demographic and clinical data were gathered for all participants such as age, sex and, in cases, date of diagnosis, FAB morphological classification (L1, L2 or L3), number of chemotherapy cycles and disease duration (time between diagnosis and study enrolment).

2.4. Laboratory Methods

All participants' venous blood samples (3-5 mL) were taken under aseptica condition. In patients with cases, the samples were collected during regular follow-up visits when patients did not have any acute complications. Blood samples were left to clot for 30 minutes at room temperature, and then centrifuged at 3000 rpm for 10 minutes to separate the serum. The standard automated colorimetric methods were used to measure the serum phosphorus on a [Analyzer Name] analyzer. The laboratory's normal range for serum phosphate was 3.0-6.0mg/dl; the age specific normal ranges were used to interpret the results.

2.5. Statistical Analysis

[Statistical Software Name] was used to analyze the data. Continuous variables were represented as mean ± SD (normally distributed data) or median (IQR) (data that were not normally distributed). Categorical variables are presented in frequencies and percentages. The normality of distribution was verified based on Shapiro-Wilk test and by histogram and Q-Q plots.

Independent samples t-test was used to compare serum phosphorus levels between cases and controls for normally distributed data; the Mann-Whitney U test was used if the data were not normally distributed. In the case group, comparisons of serum phosphorus level between categorical variables (sex, age groups, FAB classification, chemotherapy cycles, disease duration) were carried out using independent samples t-test between two groups and one-way ANOVA between multiple groups and followed by appropriate post-hoc tests as indicated. Non-parametric tests (Mann-Whitney U or Kruskal-Wallis) were used as appropriate, when the size of the subgroups was small.

Since there are physiological differences in phosphorus homeostasis and bone growth, age was analyzed both as a continuous variable and as two categories: younger children (1-8 years) and older children/adolescents (9-16 years). Data distribution and clinical relevance led to dichotomizing the number of chemotherapy cycles into <10 cycles and ≥10 cycles. The period of disease was divided into three groups: (1) 1 month to 1 year, (2) 2-4 years, and (3) 5-7 years since diagnosis.

All the analysis was considered statistically significant with a p-value <0.05. Two-tailed testing was used for all tests.

3. Results

The study comprised of fifty children with ALL (cases) and thirty healthy children (controls) aged 1–16 years. Of the 50 ALL patients, 70% (n = 35) were boys and 30% (n = 15) were girls, as is known in pediatric ALL. The ages ranged from 1 to 16 years (mean age [X.X ± X.X] years in cases and [X.X ± X.The control duration was for X] years.

Table 1 The demographic characteristics of the study participants are presented. Demographic characteristics of the study participants are given

Characteristic	Cases (n=50)	Controls (n=30)
Age (years), mean ± SD	[X.X ± X.X]	[X.X ± X.X]
Age range (years)	1-16	1-16
Sex, n (%)		
Male	35 (70%)	[X (X%)]
Female	15 (30%)	[X (X%)]

3.1. FAB Classification Distribution

The FAB morphological classification was performed in 50 ALL patients, with 43 (86%) patients classified as L1, 1 (2%) as L2, and 6 (12%) as L3. This distribution is similar to the one observed in ALL of childhood, which is known to be more L1 dominant than L2 or L3, and L3 being a small, but clinically important group.

Table 2 In ALL patients, the percentage of FAB classification distribution is shown in the bar chart

FAB Subtype	Number of Patients	Percentage
L1	43	86%
L2	1	2%
L3	6	12%
Total	50	100%

3.2. Serum Phosphorus (mg/dl) Levels: Cases versus Controls

The mean serum phosphorus level of the ALL patients was 4.4 ± 0.8 mg/dL, which is higher than the healthy controls (4.1 ± 0.6 mg/dL). The mean level of phosphorus was slightly elevated in ALL patients but not significantly (P = 0.109).

Table 3 The case and control groups were compared for differences in serum phosphorus levels. The difference in serum phosphorus level between case and control groups was compared

Group	n	Serum Phosphorus (mg/dL) Mean ± SD	P-value
ALL patients (Cases)	50	4.4 ± 0.8	0.109
Healthy controls	30	4.1 ± 0.6	

3.3. Phosphorus in the bloodstream, male vs. female.

Among ALL patients, mean serum phosphorus levels were 4.47 ± 0.84 mg/dL in boys (n=35) and 4.15 ± 0.70 mg/dL in girls (n=15). There was no statistically significant difference (P = 0.729).

Table 4 Serum Phosphorus Levels by Sex in ALL Patients

Sex	n	Serum Phosphorus (mg/dL) Mean ± SD	P-value
Boys	35	4.47 ± 0.84	0.729
Girls	15	4.15 ± 0.70	

3.4. Serum Phosphorus Levels (by age group)

A comparison of the mean serum phosphorus levels of ALL patients stratified by age revealed that younger children (1-8 years, n=[X]) had a mean phosphorus level of 4.56 ± 0.70 mg/dL, whereas older children and adolescents (9-16 years, n=[X]) had a mean phosphorus level of 4.19 ± 0.89 mg/dL. The younger children tended to be higher in phosphorus than the older ones, but this difference was not significant (P = 0.113), and may represent a normal developmental physiology.

Table 5 Serum Phosphorus Levels in ALL Patients by Ages

Age Group	n	Serum Phosphorus (mg/dL) Mean ± SD	P-value
1-8 years	[X]	4.56 ± 0.70	0.113
9-16 years	[X]	4.19 ± 0.89	

3.5. The FAB classification is used to measure serum phosphorus levels

Mean serum phosphorus levels were 4.29 ± 0.79 mg/dL in the L1 patients (n=43), 4.20 mg/dL in the single L2 patient (n=1), and 5.02 ± 0.80 mg/dL in L3 patients (n=6). Mean phosphorus level was higher in the four L3 patients, but the difference between the four FAB subtypes was not significant (P = 0.115).

Table 6 Serum Phosphorus on FAB Classification in ALL patients

FAB Subtype	n	Serum Phosphorus (mg/dL) Mean ± SD	P-value
L1	43	4.29 ± 0.79	0.115
L2	1	4.20	
L3	6	5.02 ± 0.80	

3.6. Normal serum phosphorus levels according to number of chemotherapy cycles received.

Patients who received less than 10 rounds of chemotherapy (n=[X]) were found to have a mean serum phosphorus level of 4.59 ± 0.73 mg/dL, and those who received 10 or more rounds of chemotherapy (n=[X]) had a mean serum phosphorus level of 4.27 ± 0.83 mg/dL. Between the two groups this difference was not statistically significant (P = 0.191).

Table 7 Serum Phosphorus Levels according to the number of chemotherapy cycles

Chemotherapy Cycles	Serum Phosphorus (mg/dL) Mean ± SD	P-value
<10 cycles	4.59 ± 0.73	0.191
≥10 cycles	4.27 ± 0.83	

These are the phosphorus levels in the serum of patients diagnosed with a disease, based on the duration of the disease.

Disease duration analysis revealed mean serum phosphate of 4.69 ± 0.84 mg/dL for patients one month – one year from diagnosis (n=[X]); 4.15 ± 0.82 mg/dL for patients two – four years from diagnosis (n=[X]) and 4.60 ± 0.40 mg/dL for patients five – seven years from diagnosis (n=[X]). However, although there were some differences in numbers between groups, they were not statistically significant (P = 0.083).

Table 8 Serum Phosphorus Levels according to the duration of the disease

Disease Duration	Serum Phosphorus (mg/dL) Mean ± SD	P-value
1 month - 1 year	4.69 ± 0.84	0.083
2-4 years	4.15 ± 0.82	
5-7 years	4.60 ± 0.40	

4. Summary of Results

In conclusion, there were no significant differences between the ALL patients and healthy controls, or between the different clinical subgroups (sex, age, FAB classification, chemotherapy cycles or disease duration) in the serum phosphorus levels. Mean phosphorus concentrations were in the normal range or near the normal range in all children.

5. Discussion

The present study was a case-control study involving 50 children with ALL and 30 healthy children to determine the association of serum phosphorus levels with key clinical parameters such as FAB morphological type, sex, age, number of cycles of chemotherapy, and disease duration. The mean serum phosphorus level was slightly elevated but not statistically significant in ALL patients compared to controls (4.4 ± 0.8 mg/dL vs. 4.1 ± 0.6 mg/dL, P = 0.109). Moreover, none of the clinical variables studied was significantly associated with phosphorus levels. These results indicate that in clinically stable paediatric ALL patients, during non-ALLE phases, there is a good degree of phosphorus homeostasis.

5.1. In ALL patients, serum phosphorus was compared with that of controls

Our results were similar to those of several previous studies that have studied electro-chemical profiles in stable children with leukemia, as there was no statistically significant difference in serum phosphorus levels between the ALL group and the healthy control group. Naeem et al. showed that TLS developed in a significant percentage of newly diagnosed ALL patients, but patients who developed TLS did not have significantly different levels of phosphorus during the entire course of therapy [21]. Xue et al. also reported that hyperphosphatemia in pediatric ALL occurred mainly during the acute stage of the disease and during the first course of therapy in high tumor burden patients, and that most patients had returned to normal phosphorus levels after the first course of therapy [22]. Our results confirm these observations, as even comparison of a mixed group of ALL patients throughout the treatment period with healthy controls showed mean phosphorus levels within the normal range and not significantly different from healthy controls. This implies that, in stable ALL patients treated with modern ALL schemes, the mechanisms of phosphate regulation, such as renal excretion, gut absorption and bone metabolism, are not significantly impaired.

The trend is slightly towards higher phosphorus levels in ALL patients, however (mean difference of 0.3 mg/dL), this should be considered. This observation is not statistically significant in this study, but may be a mild continued metabolic effect of the disease or treatment. These may be caused by subclinical rises in cell turnover, renal tubular failure to handle phosphorus adequately caused by chemotherapy, changes in bone metabolism due to corticosteroid administration and dietary changes or nutritional depletion during treatment. A larger study with more statistical power is required to see if this numerical difference is really a biological effect, or a random difference.

5.2. Sex Differences in Serum Phosphorus levels

In this study, there was no significant difference in serum phosphorus level between boys (4.47 ± 0.84 mg/dL) and girls (4.15 ± 0.70 mg/dL) with ALL (P = 0.729). This is somewhat unexpected, as epidemiological studies have established a sex difference in the incidence of ALL, with boys having rates of about 20-40% higher than girls [2]. The extensive epidemiological study by Kakaje et al. revealed that in ALL there was a significant difference in the demographic and clinical features between boys and girls, such as the age distribution and possibly metabolic profile [2]. Their study, however, did not actually look at levels of phosphorus based on sex. It is of interest that in our study, there were no sex differences in phosphorus levels, indicating that at this stage of disease, when it is clinically established, any biological factors that may be involved in the male predominance in the incidence of ALL do not seem to have a significant effect on phosphorus homeostasis. This is a welcome finding from a clinical management point of view as it doesn't require sex-specific monitoring strategies for phosphorus in children with ALL.

5.3. Age-related changes to serum phosphorus levels.Phosphorus pattern change with age

When comparing the serum phosphorus level in the younger children (1-8 years, mean = 4.56 ± 0.70 mg/dL) with the older children/adolescents (9-16 years, mean = 4.19 ± 0.89 mg/dL), there was no significant difference (P = 0.113), although there was a numerical trend toward higher levels in the younger children. This is in keeping with normal physiologic development and younger children usually have higher levels of serum phosphate which is needed to support rapid skeletal growth and bone mineralization. Biro et al. systematically summarized the physiology of phosphorus homeostasis in children and pointed out that age-specific reference ranges are needed to evaluate phosphorus levels in children and that normal levels progressively decrease from infancy to adolescence [23]. The age trend of our ALL patients was similar to healthy children, indicating the general developmental regulation of phosphorus metabolism is not affected by leukemia and continuous chemotherapy. This finding has clinical implications

and should be taken into account when assessing the phosgene oxime level of children with ALL, with the use of age-specific reference ranges rather than the use of a single range for all ages.

5.4. The water specimen was classified based on the FAB method. The water sample was classified according to FAB method.

The trend of increasing serum phosphorus concentration in the patients with FAB L3 subtype (5.02 ± 0.80 mg/dL) was more than the patients in FAB L1 subtype (4.29 ± 0.79 mg/dL) and FAB L2 subtype (4.20 mg/dL) but the difference was not statistically significant (P = 0.115). The L3 subtype (mature B-cell leukemia, or Burkitt leukemia) is well known for its high tumor burden, exquisite chemosensitivity, and rapid proliferation and is known to be associated with the highest risk of TLS. Hyperphosphatemia was one of the cardinal features, and L3 morphology was significantly associated with increased risk of TLS and metabolic complications in pediatric ALL patients, as reported by Al Blewi et al [24]. Elkhatib et al. also reported that patients with Burkitt leukemia/L3 ALL were found to have significantly elevated rates of TLS and electrolyte disturbances [25]. In our L3 patients, the elevated mean phosphorus concentration in the absence of any obvious TLS at the time of sampling could be related to the continued presence of higher rates of cell turnover in these patients, or to residual metabolic effects from previous TLS. Our study had few (n=6) L3 patients, and so there were limited statistical powers to detect significant differences but the direction of the effects in multiple studies prompted further consideration of increased phosphorus monitoring in L3 patients during stable treatment periods.

5.5. How many cycles of chemotherapy affects blood phosphorus levels?

No significant difference was detected between the phosphorus levels in patients who received fewer cycles of chemotherapy (<10 cycles: 4.59 ± 0.73 mg/dL) and those who received more extensive chemotherapy (≥10 cycles: 4.27 ± 0.83 mg/dL) (P = 0.191); however, there was a numerical trend toward higher phosphorus levels in less-treated patients. This could be due to a variety of mechanisms. Increased cell turnover and/or residual disease burden in patients who are earlier in treatment course may result in higher levels of phosphorus release. However, if the patient has had more chemotherapy cycles, they may have better control of the disease with less tumour burden, and therefore lower levels of phosphorus. Xiao et al. studied how metabolic parameters changed in various treatment phases in ALL and observed that electrolyte disturbances were most severe during induction therapy and tended to be restored during the maintenance phases [26]. However, Pommert et al. found that the chance of severe electrolyte disturbances such as hyperphosphatemia is significantly reduced following the first treatment period when the tumour burden is decreased and remission has been achieved [27]. In the same way, our findings were in line with this trend indicating that as treatment advanced and/or the disease was controlled, the phosphorus level became more normal.

5.6. The duration of disease and phosphorus homeostasis

An interesting pattern was observed during analysis of serum phosphorus level according to disease duration, with higher mean serum phosphorus level observed in patients 1 month to 1 year from diagnosis (4.69 ± 0.84 mg/dL), lower level in patients 2-4 years from diagnosis (4.15 ± 0.82 mg/dL), and intermediate level in patients 5-7 years from diagnosis (4.60 ± 0.40 mg/dL) (P = 0.083). This U-shaped pattern is interesting, and may represent varying stages of disease and treatment. The high levels in the first year may be due to the acute disease phase and/or the intensive phase of treatment where metabolic disturbances tend to be more frequent. The lower levels in the 2-4 year group might be a reflection of metabolic recovery and stabilization in the maintenance treatment or early surveillance following treatment. This slight elevation in the 5-7 year group is more difficult to interpret but may be late effects of treatment on bone metabolism or renal function, but caution should be applied in this subgroup due to the small sample size and wide confidence interval. In their study of longterm metabolic consequences in pediatALL survivors, Matinyan et al. mentioned that persistent changes in mineral metabolism may not occur until years after the completion of therapy [28]. A similar study by Afrin et al. showed that the exposure of children with leukemia to cumulative treatment and disease duration may have an impact on several metabolic parameters [29]. Serial phosphorus measurements across the disease course would be useful in larger longitudinal studies to further define these time trends.

These overall results suggest that there is no significant difference between the level of serum phosphorus in the patients with stable ALL and healthy controls, and that there were no strong associations between serum phosphorus and clinical variables; these findings have important implications for clinical practice and for resource allocation. All these results indicate that frequent and regular monitoring of the phosphorus level may not be required in all ALL patients during all phases of their treatment. Rather, a risk-stratified, phase appropriate monitoring of phosphorus seems most appropriate. Intensive monitoring should be used during high-risk periods such as initial diagnosis (in patients with high WBC count, bulky disease and L3 morphology), beginning of chemotherapy and any relapse or intensification of treatment. Perissinotti et al., in their extensive guidelines for TLS prevention and management,

suggested that with high-risk patients, electrolyte monitoring is needed on a daily basis and for low-risk patients, less frequent monitoring is acceptable [30]. The British Society for Haematology guidelines by Chan et al. also recommended a risk adapted approach to monitoring TLS and the level of laboratory monitoring should be adjusted according to the risk factors of each patient [31]. These results are in line with the risk stratification approach and show that routine monitoring of phosphorus in stable ALL patients in maintenance therapy and in long-term follow-up is not necessary unless there are clearly defined clinical indications.

It is important to note, however, that in stable patients, the lack of a significant abnormality of phosphorus does not mean that complacency should be assumed in high-risk periods. The relatively normal phosphorus levels found in our study population may be due to good patient selection (acute TLS excluded), good prophylactic precautions, and good management of high-risk periods. Sustaining this positive result depends on ongoing implementation of TLS prevention and monitoring measures during critical times [30,31].

5.7. Strengths and Limitations

The advantages of this study are that a healthy control group was used to compare, more than one clinically significant variable was studied, and the analytical method used for the measurement of phosphorus was standardized. The study offers valuable information about the maintenance of phosphorus balance in a real world population of children with ALL in various phases of therapy.

Some drawbacks should be noted, however. First, the design of the cross section leaves one without the ability to evaluate time-dependent changes in the level of phosphorus in individual patients. More complete information regarding phosphorus dynamics could be provided by longitudinal studies with serial measurements. Second, sample size for the primary comparison between cases and controls was sufficient, but was small for analyses of subgroups, including the L2 subtype (n=1) and some of the disease duration groups. This small sample size resulted in limited statistical power to detect small yet clinically significant differences. Third, data on detailed concurrent medications, nutritional status, renal function parameters, or bone metabolism markers were not available, which may give insights into the mechanism of action and influence the levels of phosphorus. Fourth, this study was performed at one center, so the findings might not be generalizable to other populations or treatment contexts. Fifth, our study was conducted in stable patients and excluded patients with an acute TLS or metabolic crisis, meaning that results from our study do not provide information on phosphorus levels when the monitoring is most critical, during high-risk acute phases of the disease.

5.8. Future Research Directions

Further studies are needed to answer several key questions. Additional diagnostic to treatment completion and long-term survivorship data on phosphorus levels in serial blood draws would be helpful in determining time trends and times of highest risk for abnormalities. Higher powered multi-center trials with sufficient numbers for sub-group analysis may clearly identify specific patient sub-populations (e.g. L3 patients or those with specific genetic sub-types) with specific phosphorus profiles and appropriate patient monitoring strategies. A more comprehensive metabolic profile, combined with the measurement of phosphate, would offer a more holistic understanding of mineral homeostasis in pediatric ALL, and facilitate future study of the relationship between phosphate and the other minerals, as well as between phosphate and markers of bone and renal function. Monitoring of phosphorus levels for possible association with clinical parameters such as treatment related toxicity, bone health, and long term complications could be used to identify if there is a prognostic role beyond immediate TLS risk assessment. Finally, as novel therapies such as targeted agents and immunotherapies continue to be part of the treatment options in Paediatric ALL, studies of the effects of these new therapies on phosphorus homeostasis would be useful [31].

6. Conclusion of Discussion

To summarize, in clinically stable children with ALL, no significant differences in serum phosphorus levels were noted when compared with healthy children and no significant correlation was found between serum phosphorus and sex, age, FAB classification, duration of chemotherapy or disease duration. This study indicates that the phosphorus homeostasis is fairly intact during stable ALL without acute tumor lysis. This may not, however, be a reason to decrease surveillance during the high-risk periods when hyperphosphatemia can still be a life-threatening complication that needs close monitoring and timely correction. A risk-stratified, phase-appropriate approach to phosphorus monitoring seems to be most suited to optimising care, and the efficient use of resources in the management of ALL.

7. Conclusion

This case-control study included the serum phosphorus level of 50 children with ALL and 30 healthy controls, and the correlation between the level of serum phosphorus and clinical parameters such as sex, age, FAB classification, chemotherapy cycles, and duration of disease. The study revealed that the mean level of serum phosphorus was slightly higher in ALL patients (4.4 ± 0.8 mg/dL) than in controls (4.1 ± 0.6 mg/dL) without being statistically significant (P = 0.109). There were no significant correlations between the level of phosphorus and the clinical parameters studied. The results indicated that in the clinically stable pediatric ALL patients (outside acute tumor lysis period) the homeostasis of phosphorus is relatively well preserved. Results suggest that there is little variation between clinical subgroups, suggesting that the mechanisms regulating phosphorus are preserved in the stable treatment periods. But the results should not take precedence over the need to monitor carefully during periods of high risk, such as initial diagnosis, when treatment is first initiated and when the disease recurs, when there is still a risk of tumour lysis and high levels of phosphate. The study supports a risk-stratified, phase appropriate strategy for monitoring of phosphorus in paediatric ALL, namely the use of intensive monitoring during high-risk phases and patients and a more relaxed approach during stable phases such as maintenance. More detailed metabolism profiling in future longitudinal studies with larger patient numbers would further elucidate the role of phosphorus in the course of ALL to further optimise monitoring strategies and improve patient outcome whilst efficiently using health care resources.

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