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Renal phosphate loss in Iraqi chronic myeloid leukemia patients treated by imatinib mesylate

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Abstract:

BACKGROUND: The use of BCR-ABL tyrosine kinase inhibitor imatinib mesylate improved outcomes for patients with chronic myeloid leukemia (CML). Hypophosphatemia is found to be associated with imatinib mesylate use; the exact mechanism of this is not clear yet but mostly related to a drug-induced proximal renal tubular defect.

OBJECTIVE: The objective was to measure the renal phosphate loss in CML patients treated by imatinib mesylate.

PATIENTS AND METHODS: A cross-sectional study included 40 patients (25 females) who were already diagnosed cases and treated with imatinib mesylate (400 mg/day). The mean age was 40.2 ± 7.8 years. The study was conducted at the medical city teaching hospital, Baghdad, hematology outpatient clinic from July 2016 to December 2016. Serum and random urine samples were measured phosphate and creatinine in serum and urine, respectively. Serum and urine phosphate were measured using the colorimetric method, whereas serum and urine creatinine were calculated by the kinetic method. Fractional excretion of phosphate and tubular maximum of phosphate reabsorption were calculated. After the completion of the study, we tested ten newly diagnosed patients at 0- and 3 months of treatment.

RESULTS: Sixteen patients (40%) developed hypophosphatemia. The fractional excretion of phosphate increased (FEPO4 = 21.1%) with a comparable reduction in tubular reabsorption of phosphate to the glomerular filtration rate (Tmpi/GFR = 2.3 mg/dl). There was a significant direct correlation between SPO4 level and white blood cell count (R = 0.451; *P* = 0.001). The mean intact parathyroid hormone and Vitamin D levels were normal for the study group. All ten newly diagnosed cases developed hypophosphatemia at 3 months. This was statistically significant (*P* = 0.002). There increase in FEPO4 and decrease in Tmpi/GFR was statistically significant (*P* < 0.001 and 0.002), respectively.

CONCLUSION: Hypophosphatemia while using imatinib mesylate is due to increased urinary phosphate excretion.

Keywords:

Chronic myeloid leukemia, hypophosphatemia, imatinib mesylate

Introduction

Phosphate (one of the most abundant anions in mammals) is crucial for bone mineralization and cellular activity.[1]

Reabsorption of phosphate filtered by the glomerulus occurs almost exclusively in the renal proximal tubule and is an active, hormonally regulated process.[2] Both the fibroblast growth factor-23 (FGF23) and parathyroid hormone (PTH) the main phosphaturic agents. FGF-23 (a hormone produced mainly by bone and connective tissue that inhibits reabsorption of phosphate by the kidney) and PTH (which also decreases renal phosphate reabsorption).[1]

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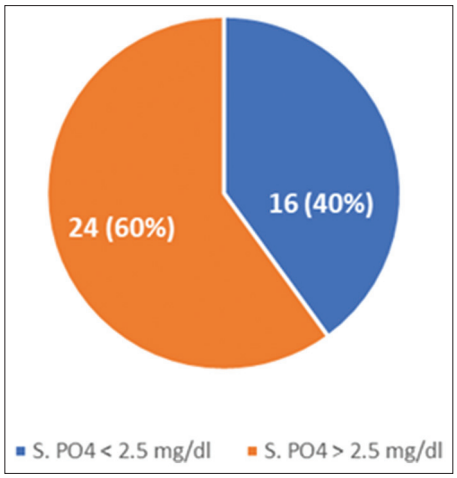

Figure 1: Hypophosphatemia in chronic myeloid leukemia patients using imatinib mesylate

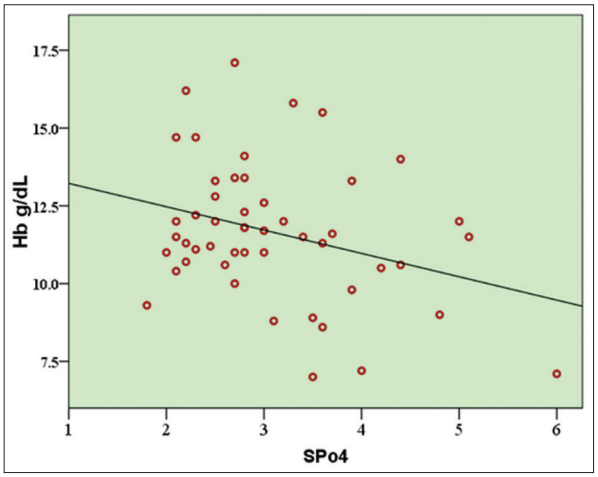

Figure 2: Inverse correlation between SPO4 and Hb tested by the linear regression test

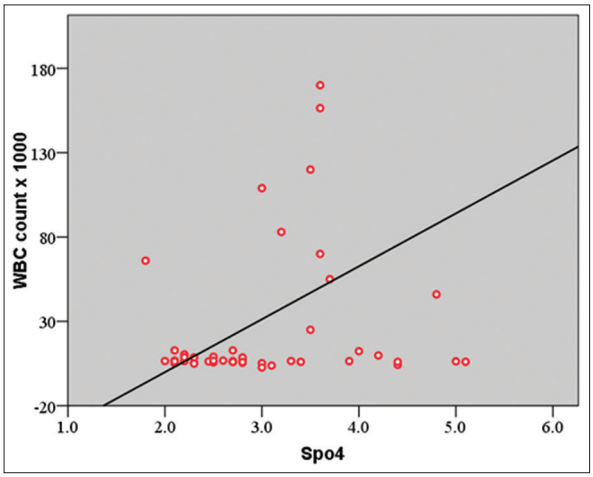

Figure 3: Direct correlation between SPO4 and white blood cell count tested by the linear regression test

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm associated with the Philadelphia chromosome t(9;22) (q34;q11), the resultant *BCR-ABL1* fusion gene, and the constitutively active tyrosine kinase BCR-ABL1. In the absence of treatment, CML has a triphasic or biphasic clinical course, as it progresses from a chronic phase to an accelerated phase and on to a terminal blast crisis.[3]

Imatinib mesylate is the first member of tyrosine kinase inhibitors (TKIs) used for the treatment of patients with the chronic phase of CML. It has proven remarkably efficient in the treatment of gastrointestinal stromal tumors (GISTs) and other myeloproliferative diseases. It also used for the treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia.[4]

It is conceivable that reduced levels of phosphate seen in imatinib-treated patients could result from one or a combination of the following mechanisms: decrease intestinal absorption of phosphate, increase urinary loss of phosphate, decrease the dissolution of phosphate from bone, or sequestration of phosphate from the extracellular fluid into the bone. Nonetheless, imatinib therapy is associated with decreased reabsorption of phosphate by the kidneys, suggesting that increase renal phosphate output may be the cause of the observed decrease in serum phosphate.[5,6] In addition, imatinib may be associated with more nonselective proximal tubulopathy with aminoaciduria.[7]

Osorio *et al*. reported that hypophosphatemia occurs not only in the context of imatinib use but also the occurrence of hypophosphatemia is associated with major genetic response in CML patients treated with such TKI.[8]

The aim of this study is to measure renal phosphate loss as a cause of hypophosphatemia in CML patients treated by imatinib mesylate.

Patients and Methods

Setting and study design

A cross-sectional study was conducted in the medical city teaching complex, Baghdad, from July 2016 to December 2016.

Ethical consideration

The proposal of this study was made according to the research ethics code of the Iraqi MOH and the scientific board of internal medicine in the Arab Board of Health Specializations in Iraq. All participants signed a written consent form explaining the study objectives, and all data were kept confidential during all stages of the work.

Definition of the participant inclusion and exclusion criteria

The study included 40 CML patients diagnosed by bone marrow aspiration and biopsy and fluorescence *in situ*

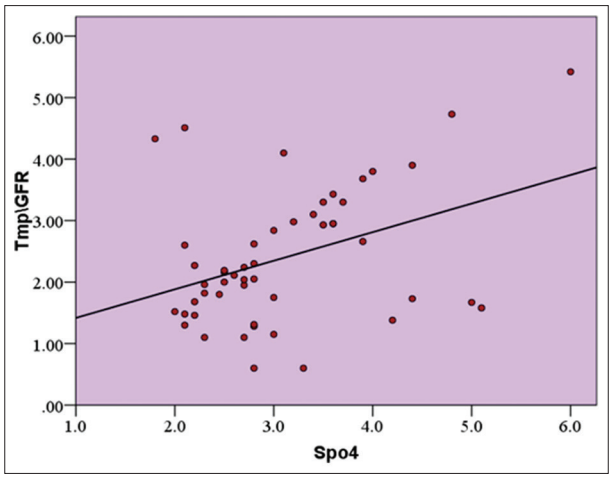

Figure 4: Direct correlation between SPO4 and tubular reabsorption of phosphate to the glomerular filtration rate tested by the linear regression test

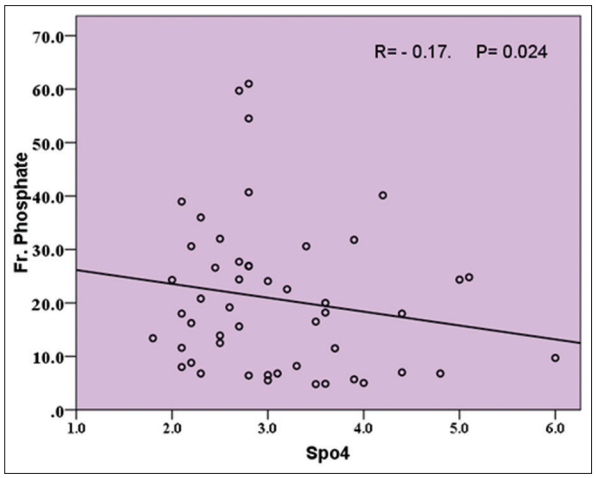

Figure 5: Inverse correlation between SPO4 and FEPO4 tested by the linear regression test

hybridization study in the chronic phase. The duration of disease ranges from 1 to 10 years, and they were already treated by imatinib mesylate (400 mg/day).

Exclusion criteria

Diabetes mellitus, hypertension, heart failure, renal impairment, using drugs that cause hypophosphatemia (antacid, diuretics, steroids, salbutamol, acyclovir, intravenous iron, erythropoietin, and granulocyte-macrophage colony-stimulating factor), history of chronic diarrhea, and alcoholism. Patients with a history of parathyroid disease and patients in blastic crises and accelerated phases of CML were excluded from the study.

Sampling

All study participants recruited consecutively, as they attended the hematology outpatient clinic in Baghdad teaching hospital. With the application of exclusion criteria, the participants were selected conveniently.

Protocol

All patients were interviewed and examined, and all records were reviewed. Blood and urine phosphate samples were measured. Fractional urinary excretion and tubular maximum of phosphate reabsorption were measured.

Measurement

Fasting serum phosphorus (NR 2.5–4.5 mg/dl) and serum creatinine (NR 0.6–1.2 mg/dl) were measured using spectrophotometry Cecil CE 1011 (UK), at the nephrology and renal transplant center, the medical city, Baghdad. The random urine sample was used to measure urine phosphate and urine creatinine. Serum phosphate and urine phosphate were calculated by the colorimetric method, whereas serum and urine creatinine were calculated by the kinetic method.

Fractional excretion of phosphate was calculated using the following equation:

FEPO4 (%) = (urine phosphate × plasma creatinine/plasma phosphate × urine creatinine) × 100

A daily phosphate excretion of <3.2 mmol (100 mg) and fractional excretion of phosphate <5% (the normal value was 15%–20%) allow the diagnosis of nonrenal phosphate loss. A urinary phosphate excretion >3.2 mmol (100 mg) or a fractional excretion >5% is indicative of renal phosphate wasting.[9]

The tubular maximum for phosphate reabsorption was calculated using the following equation:

Tubular reabsorption of phosphate to the glomerular filtration rate (Tmpi/GFR) (mg/dl) = plasma phosphate − (urine phosphate × plasma creatinine/urine creatinine).

TmPi is correlated to the GFR level; therefore, its value had been estimated using the Bijvoet nomogram.[10]

Other laboratory data were measured and recorded, including the hematology panel, serum calcium, and alkaline phosphatase, Vitamin D, and iPTH. At the time of the conduction of the study, the test for FGF23 was not available.

Outcome

The outcome was low serum phosphate with increased urinary excretion of phosphate and reduced tubular phosphate reabsorption.

Extension of the study

After completion of the study, we tested ten newly diagnosed patients at 0- and 3-month time of treatment.

Table 1: Comparison of baseline versus 3-month follow-up parameters of the ten new cases

Parameters	Baseline		After 3 months		*t***	*P**
	Mean	SD	Mean	SD		
Serum PO4 (mg/dl)	4.0	0.9	2.8	0.6	−3.62	0.002
FEPO4 (%)	9.8	6.0	29.4	9.1	5.70	<0.001
Tmpi/GFR (mg/dl)	3.4	1.1	2.0	0.6	−3.59	0.002
WBC ($\times 10^9$/l)	126.6	36.3	8.7	1.4	−3.87	0.001
Platelets ($\times 10^9$/l)	235.5	61.9	236.5	31.5	0.01	0.989
Hemoglobin (g/L)	9.7	2.7	10.8	0.9	1.26	0.224
Serum calcium (mmol/l)	1.0	0.1	1.0	0.02	−1.88	0.076
Serum ALP (U/L)	61.5	20.1	50.4	13.1	−1.47	0.160
Serum creatinine (mg/dl)	0.9	0.2	1.0	0.1	1.35	0.194

*P <0.05. SD: Standard deviation, GFR: Glomerular filtration rate, WBC: White blood cell, ALP: Alkaline phosphatase, Tmpi/GFR: Tubular reabsorption of phosphate to the glomerular filtration rate

Statistical analysis

The statistical analysis was performed by the IBM Corp. Released in 2013. IBM SPSS Statistics for Windows, version 22.0. Armonk, NY, USA: IBM Corp.

Data of all participants were entered and analyzed with appropriate statistical tests. Descriptive statistics were presented as a mean and standard deviation for the continuous variables and as frequencies and proportions for the categorical variables (number and percentage). Analysis of variances F-test was used to compare means of variables for the study groups, and Student's *t*-test was used to compare means for two groups. Bivariate Pearson's correlation test was used to estimate the significance of the correlation between SPO4 and other parameters. Pearson's correlation coefficient (R) value represented the strength of the correlation, and the sign of R represented the direction of the correlation as followed: $R < 0.4$ indicated a mild correlation, $R = 0.4–0.7$ indicated a moderate correlation, and $R > 0.7$ indicated a strong correlation. The minus signed R indicated an inverse (negative) correlation, and the no sign (positive) R-value indicated a positive (direct) correlation. Linear regression (curve estimation) was used to assess the significance and direction of the correlation between SPO4 and other variables separately. The level of significance (P value) was set at ≤ 0.05 as a cutoff point for significant difference or correlation, $P < 0.001$ indicated a highly significant difference or correlation. Finally, results and findings were presented in tables, figures, or graphs with an explanatory paragraph.

Results

The study recruited 40 patients (25 females) with CML, with a mean age of 40.2 ± 7.8 years. The mean duration of CML was 3.7 + 2.6 (range: 1–10) years. Sixteen patients (40%) developed hypophosphatemia [Figure 1]. The mean iPTH was (61.5 + 3.81 pg/ml), and the mean Vitamin D was (21.9 + 5.6 ng/ml).

Discussion

This study shows that treatment with imatinib mesylate is associated with hypophosphatemia, mostly due to increased renal excretion.

Forty percent (16/40) of patients treated with imatinib mesylate developed hypophosphatemia. This was consistent with the results from Osorio *et al*., whereas 39% of the patients develop hypophosphatemia. Joensuu and Richardt reported that 80% of their patients showed hypophosphatemia on at least one occasion during imatinib treatment.[8]

The mean SPO4 level (2.89 mg/dl) remains within the normal range despite the high level of FEPO4, which is similar to the results found by Berman *et al*. and was explained by early proximal tubular dysfunction.[11]

Under normal physiological conditions, the FEPO4 varies between 5% and 20%. In this study, the mean FEPO4 was 23.4%, the mean Tmpi/GFR (2.13 mg/dl) was low (range 2.8–4.4). The decrease in Tmpi/GFR (that should be high in this context as a compensatory response to hypophosphatemia) indicates that the PO4 losses are produced within the kidney.[12]

The reduction in SPO4 level was in association with a hematological response (normalization of blood counts and resolution of disease-associated symptoms) [Figures 2 and 3].[13]

The renal loss could be due to an imatinib-induced tubulopathy, selective for PO4 losses, or to a more generalized dysfunction.[7] Most of the previous studies did not use Tmpi/GFR, except one case reported by Helene François and Paul cope at which they use Tmpi/GFR as an indicator of phosphate loss,[14] we failed to found other studies used both FEPO4 and Tmpi/GFR as a better indicator of renal phosphate wasting [Figures 4 and 5].

Imatinib may alter bone remolding even in patients with normal serum phosphate.[11] We were unable to study such effect in the absence of laboratory tests for markers of bone formation and resorption.

Such renal wasting has been reported in cancers other than CML like GISTs. In addition to bone remodeling, it may be a class effect of TKIs.[15,16]

This study limited by the unavailability of laboratory testing FGF23. At the time of conduction of the study, the second-line TKIs for the treatment of CML patients in Iraq were not available.

In the newly diagnosed cases, SPO4 level was significantly reduced after 3 months of treatment with imatinib mesylate (the mean SPO4 at baseline was 4.0 ± 0.9 reduced to 2.8 ± 0.6; $P = 0.002$) [Table 1]. This result is consistent with previous studies that measured the SPO4 level and found a significant reduction in SPO4 level after treatment with imatinib mesylate.[10] The reduction in the SPO4 level was in association with a hematological response (normalization of blood counts and resolution of disease-associated symptoms).[13]

Conclusion

Hypophosphatemia in the context of treatment with imatinib mesylate is due to increased urinary phosphate excretion. This may be due to drug-induced proximal tubulopathy selective for phosphate or a more generalized tubulopathy. This is mostly occurred in the first 3 months of therapy and may coincide with clinical remission. Patients on long-term imatinib treatment need monitoring for renal function as well as proximal tubule dysfunction, including hypophosphatemia.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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