

ORIGINAL ARTICLE

Altered Bone and Mineral Metabolism in Patients Receiving Imatinib Mesylate

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ABSTRACT

BACKGROUND

Imatinib mesylate inhibits several tyrosine kinases, including BCR-ABL, the C-KIT receptor, and the platelet-derived growth factor receptors α and β , all of which are associated with disease. We observed that hypophosphatemia developed in some patients with either chronic myelogenous leukemia or gastrointestinal stromal tumors who were receiving imatinib.

METHODS

We identified 16 patients who had low serum phosphate levels and 8 patients who had normal serum phosphate levels, all of whom were receiving imatinib. We performed the following biochemical measurements: whole-blood levels of ionized calcium, plasma levels of intact parathyroid hormone, and serum levels of total calcium, phosphate, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, magnesium, and markers of bone formation (bone alkaline phosphatase and osteocalcin) and bone resorption (N-telopeptide of collagen cross-links); urinalysis; and phosphate, calcium, and creatinine levels in "spot" urine specimens.

RESULTS

Patients in the low-phosphate group (median serum phosphate level, 2.0 mg per deciliter [0.6 mmol per liter]; normal level, >2.5 mg per deciliter [0.8 mmol per liter]) had elevated parathyroid hormone levels and low-to-normal serum calcium levels, were younger, and were receiving a higher dose of imatinib than patients in the normal-phosphate group (median level, 3.2 mg per deciliter [1.0 mmol per liter]). Both groups had high levels of phosphate excreted in the urine and markedly decreased serum levels of osteocalcin and N-telopeptide of collagen cross-links.

CONCLUSIONS

Hypophosphatemia, with associated changes in bone and mineral metabolism, develops in a proportion of patients taking imatinib for either chronic myelogenous leukemia or gastrointestinal stromal tumors. The drug may inhibit bone remodeling (formation and resorption), even in patients with normal serum phosphate levels.

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IMATINIB MESYLATE (GLEEVEC, NOVARTIS) inhibits several tyrosine kinases associated with disease. These enzymes include BCR-ABL in patients with chronic myelogenous leukemia (CML), C-KIT in patients with gastrointestinal stromal tumors, and platelet-derived growth factor (PDGF) receptors α and β in patients with certain myeloproliferative disorders and dermatofibrosarcoma protuberans, respectively.¹ Most patients appear to tolerate imatinib well, and no consistent metabolic abnormalities during routine electrolyte screening have been reported.² However, we noted that hypophosphatemia (a serum phosphate level of less than 2.5 mg per deciliter [0.8 mmol per liter]) developed in some patients with newly diagnosed CML who began imatinib therapy as part of a clinical trial.³ We subsequently performed biochemical evaluations in 16 patients with hypophosphatemia who were receiving imatinib (8 with CML and 8 with gastrointestinal stromal tumors), 8 patients with normal serum phosphate levels who were receiving imatinib (all with gastrointestinal stromal tumors), and 14 healthy adult volunteers.

METHODS

STUDY PATIENTS

In order to identify patients with low serum phosphate levels, we obtained a waiver of authorization from our investigational review board to review the pharmacy records of patients who were given a prescription for imatinib between April 2002 and July 2003. Patients with gastrointestinal stromal tumors and normal serum phosphate levels, as well as healthy adult volunteers who served as internal controls, were studied according to protocols approved by the investigational review board. All patients and controls provided informed written consent. We performed the following biochemical measurements in the patients and controls: whole-blood levels of ionized calcium, plasma levels of intact parathyroid hormone (PTH), and serum levels of total calcium, phosphate, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, magnesium, and markers of bone formation (bone alkaline phosphatase and osteocalcin) and bone resorption (N-telopeptide of collagen cross-links); urinalysis; and phosphate, calcium, and creatinine levels in "spot" urine specimens. Twelve of the 16 patients with hypophosphatemia, 6 of the 8 patients with normal serum phosphate levels,

and 10 of the 14 controls had blood and urine obtained between 9 a.m. and noon when they were not fasting; the remaining participants had samples taken after noon. Once identified, patients with hypophosphatemia began oral phosphate replacement (Neutra-Phos, Ortho-McNeil Pharmaceutical) at a dosage of 250 mg four times per day.

BIOCHEMICAL ASSAYS

All serum and urine assays were performed in the Clinical Chemistry Laboratory at Memorial Sloan-Kettering Cancer Center in New York. The coefficient of variation from the median value of the reference range (unless otherwise noted) was used to calculate the differences between assays.

Serum phosphate levels were determined by means of a time-rate method with acidified ammonium molybdate, and total serum calcium levels were measured with the use of an ion-specific electrode. These samples were analyzed on a Beckman LX20 analyzer and had a variance of less than 3 percent. Ionized calcium was measured with the use of an ion-specific electrode and a Nova Biomedical Stat Profile Critical Care Xpress analyzer.

Osteocalcin levels in serum treated with heparin were measured with the use of a chemiluminescent immunometric assay with an Immulite analyzer (Diagnostic Product Corporation). This assay measures the intact osteocalcin molecule only; it does not detect fragmented forms. Intact PTH was measured in plasma anticoagulated with EDTA with the use of a solid-phase two-site chemiluminescent enzyme-labeled immunometric assay with the Immulite analyzer. The osteocalcin assay had a between-assay variance of 4.5 percent, and the PTH assay had a between-assay variance of 5.2 percent.

The serum level of bone-specific alkaline phosphatase was measured with an immunoassay involving a microtiter strip (Quidel); the between-assay variance was 5.4 percent. Serum levels of N-telopeptide of collagen cross-links were measured with the use of a competitive-inhibition enzyme-linked immunosorbent assay (Wampole Laboratories) and were reported in nanomoles of bone collagen equivalents per liter. The between-assay variance was 6.9 percent. Serum levels of 25-hydroxyvitamin D were determined with an iodine-125-labeled radioimmunoassay after rapid extraction of 25-hydroxyvitamin D from the serum with acetonitrile and with the use of re-

agents supplied by DiaSorin. The between-assay variance from the mean 25-hydroxyvitamin D level of 33 ng per milliliter (82 nmol per liter) was 9.1 percent. 1,25-Dihydroxyvitamin D was quantitated in serum with a ^{125}I -labeled radioimmunoassay after purification by means of immunoextraction (ImmunoDiagnostic Systems).

The fractional excretion (FE) of phosphate was calculated by the following equation⁴:

$$FE_{\text{PO}_4} = [(U_{\text{PO}_4}) (P_{\text{Cr}}) \times 100] \div [(P_{\text{PO}_4}) (U_{\text{Cr}})],$$

where U refers to the urinary levels and P to the plasma levels of phosphate (PO_4) and creatinine (Cr).

STATISTICAL ANALYSIS

The Wilcoxon rank-sum statistic was used to compare variables among the patient and control groups.⁵ To determine whether there were pairwise associations among phosphate, PTH, both forms of vitamin D, and calcium in serum of patients with hypophosphatemia, a correlation analysis was performed. Owing to the small number of patients, we used permutation tests.⁶ For each pair, 2000 permutation resamples were generated and the P value was based on the achieved significance level.

RESULTS

STUDY PATIENTS

A total of 77 patients taking imatinib formed the basis of this study. The records of 63 patients (48 with CML, 13 with gastrointestinal stromal tumors, and 2 with other forms of sarcoma) were reviewed retrospectively to determine the incidence of hypophosphatemia. In addition, 14 patients with gastrointestinal stromal tumors were analyzed prospectively to identify patients with normal serum phosphate levels. In all, 49 patients (32 patients with CML, 16 patients with gastrointestinal stromal tumors, and 1 with another form of sarcoma) had at least one serum phosphate measurement taken; 25 of these patients (51 percent) had hypophosphatemia (15 with CML, 9 with gastrointestinal stromal tumors, and 1 with another form of sarcoma). Sixteen of the 25 patients with hypophosphatemia (8 with CML and 8 with gastrointestinal stromal tumors) continued their care at our hospital and constituted the 16 patients in the low-phosphate group who underwent further biochemical evaluations. Eight of the 14 pa-

tients with gastrointestinal stromal tumors who were studied prospectively constituted the normal-phosphate group that underwent further biochemical evaluations. The 14 controls were 7 men and 7 women (all premenopausal) with a median age of 40 years. None of the controls were taking vitamin supplements.

BIOCHEMICAL EVALUATIONS

Results of the biochemical evaluations are shown in Table 1. The median phosphate level was significantly lower in the low-phosphate group than in the normal-phosphate group (2.0 vs. 3.2 mg per deciliter [0.6 vs. 1.0 mmol per liter], $P < 0.001$). Other characteristics that differed significantly between the low-phosphate group and the normal-phosphate group included median age (50 vs. 63 years, $P = 0.02$), median daily dose of imatinib (600 vs. 350 mg, $P = 0.01$), and median PTH level (84 vs. 42 pg per milliliter, $P < 0.001$). Patients in the low-phosphate group tended to have serum total calcium values that were lower than those in patients in the normal-phosphate group (median, 8.7 vs. 9.2 mg per deciliter [2.8 vs. 3.0 mmol per liter]; $P = 0.05$). The difference in serum total calcium was particularly apparent when the low-phosphate group was compared with the control group (8.7 vs. 9.4 mg per deciliter [2.2 vs. 2.4 mmol per liter]; $P < 0.001$). Patients in the low-phosphate group also tended to have low levels of 25-hydroxyvitamin D (for eight patients, less than 20 ng per milliliter [50 nmol per liter] [see the Supplementary Appendix, available with the full text of this article at www.nejm.org]), although the median values did not differ significantly from those in the normal-phosphate group (median, 18.8 vs. 28.8 ng per milliliter [46.9 vs. 71.9 nmol per liter]; $P = 0.17$).

Both the low-phosphate and normal-phosphate groups had elevated fractional excretion of phosphate in the urine (median, 24 percent and 27 percent, respectively; $P = 0.62$); both percentages were significantly higher than those for the control group (16 percent; $P = 0.03$ and $P = 0.04$, respectively) and higher than the percentage that normally would be expected in the setting of hypophosphatemia (less than 5 percent).⁷

The median osteocalcin levels were decreased in both the low-phosphate group and the normal-phosphate group (2.3 and 3.3 ng per milliliter, respectively; $P = 0.14$), as compared with the control group (8.4 ng per milliliter; $P < 0.001$ and

Table 1. Results of Metabolic Evaluations of Patients with Hypophosphatemia and Those without Hypophosphatemia Taking Imatinib and of Controls.

Variable*	Low-Phosphate Group (N=16)	Normal-Phosphate Group (N=8)	P Value	Control Group (N=14)	P Value†	P Value‡
Median age (yr)	50	63	0.02	40	0.05	<0.001
Daily imatinib dose (mg)						
Median	600	350	0.01	—	—	—
Range	400–800	100–800				
Serum total calcium (mg/dl)						
Median	8.7	9.2	0.05	9.4	<0.001	0.10
Range	8.1–9.5	8.7–9.6		8.7–10.1		
Serum phosphate (mg/dl)						
Median	2.0	3.2	<0.001	3.5	<0.001	0.09
Range	1.0–2.4	2.7–4.0		2.8–4.1		
Fractional excretion of phosphate (%)						
Median	24	27	0.62	16	0.03	0.04
Range§	4–45	2–31		8–24		
Serum parathyroid hormone (pg/ml)						
Median	84	42	<0.001	43	<0.001	0.54
Range	41–139	27–60		15–57		
Serum 25-hydroxyvitamin D (ng/ml)						
Median	18.8	28.8	0.17	24.4	0.35	0.37
Range	3.7–97.3	16.5–40.2		11.5–56.9		
Serum 1,25-dihydroxyvitamin D (pg/ml)						
Median	59	63	0.91	63	0.88	0.96
Range	13–103	31–71		29–105		
Serum N-telopeptide of collagen cross-links (nmol of bone collagen equivalents/liter)						
Median	8.3	10.1	0.34	15.1	0.001	0.04
Range	3.0–13.4	5.3–16.0		9.1–19.4		
Serum osteocalcin (ng/ml)						
Median	2.3	3.3	0.14	8.4	0.001	0.01
Range	NMA–6.7	1.4–10.0		<1–23.4		
Serum bone alkaline phosphatase (U/liter)						
Median	20	22	0.90	25	0.10	0.24
Range	15–53	13–36		17–48		

* The Wilcoxon rank-sum statistic was used to compare variables among the patient and control groups. NMA denotes no measurable amount. To convert the values for serum calcium to millimoles per liter, multiply by 0.250. To convert the values for serum phosphate to millimoles per liter, multiply by 0.3229. To convert the values for 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.496. To convert the values for 1,25-dihydroxyvitamin D to nanomoles per liter, multiply by 2.599.

† P values are for the comparison of the low-phosphate group with the control group.

‡ P values are for the comparison of the normal-phosphate group with the control group.

§ Urinary excretion of phosphate should be less than 5 percent in the setting of hypophosphatemia.⁷

$P=0.01$, respectively). Similarly, levels of serum N-telopeptide of collagen cross-links were low in the low-phosphate group and the normal-phosphate group (8.3 and 10.1 nmol of bone collagen equivalents per liter, respectively; $P=0.34$), as compared with the control group (15.1 nmol of bone collagen equivalents per liter; $P=0.001$ and $P=0.04$, respectively). There was no significant difference in the median serum bone alkaline phosphatase level between the low-phosphate group and the normal-phosphate group (20 and 22 U per liter, respectively; $P=0.90$) or between each group of patients and the control group (25 U per liter; $P=0.10$ and $P=0.24$, respectively).

Four of the eight patients with CML were treated according to a protocol that followed serum phosphate levels prospectively. All four had normal phosphate levels before treatment. Hypophosphatemia developed 0.3, 0.5, 1.6, and 4.4 months after they started imatinib therapy.

A correlation analysis was performed in the patients with hypophosphatemia. The analysis involved comparisons of phosphate with calcium, PTH, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D, as well as PTH with calcium and both forms of vitamin D (Table 2). Although the number of observations was small, hypophosphatemia was associated with low serum levels of 25-hydroxyvitamin D ($P=0.005$), 1,25-dihydroxyvitamin D ($P=0.04$), and calcium ($P=0.009$).

DISCUSSION

In this study, hypophosphatemia and a series of associated changes in bone and mineral metabolism occurred in some patients receiving imatinib for either CML or gastrointestinal stromal tumors. Although a smaller number of patients with normal phosphate levels were studied, it appears

that many of these patients also had similar changes in bone turnover (see the Supplementary Appendix), suggesting that imatinib may affect bone despite the presence of normal serum phosphate values. The data also suggest that hypophosphatemia may be related to the patient's age and the dose of imatinib. However, among patients with normal phosphate levels, the three lowest serum osteocalcin levels were observed in patients taking either 300 or 400 mg per day (see the Supplementary Appendix). Hypophosphatemia may develop quickly; two patients were noted to have low serum phosphate levels within two weeks after starting imatinib therapy.

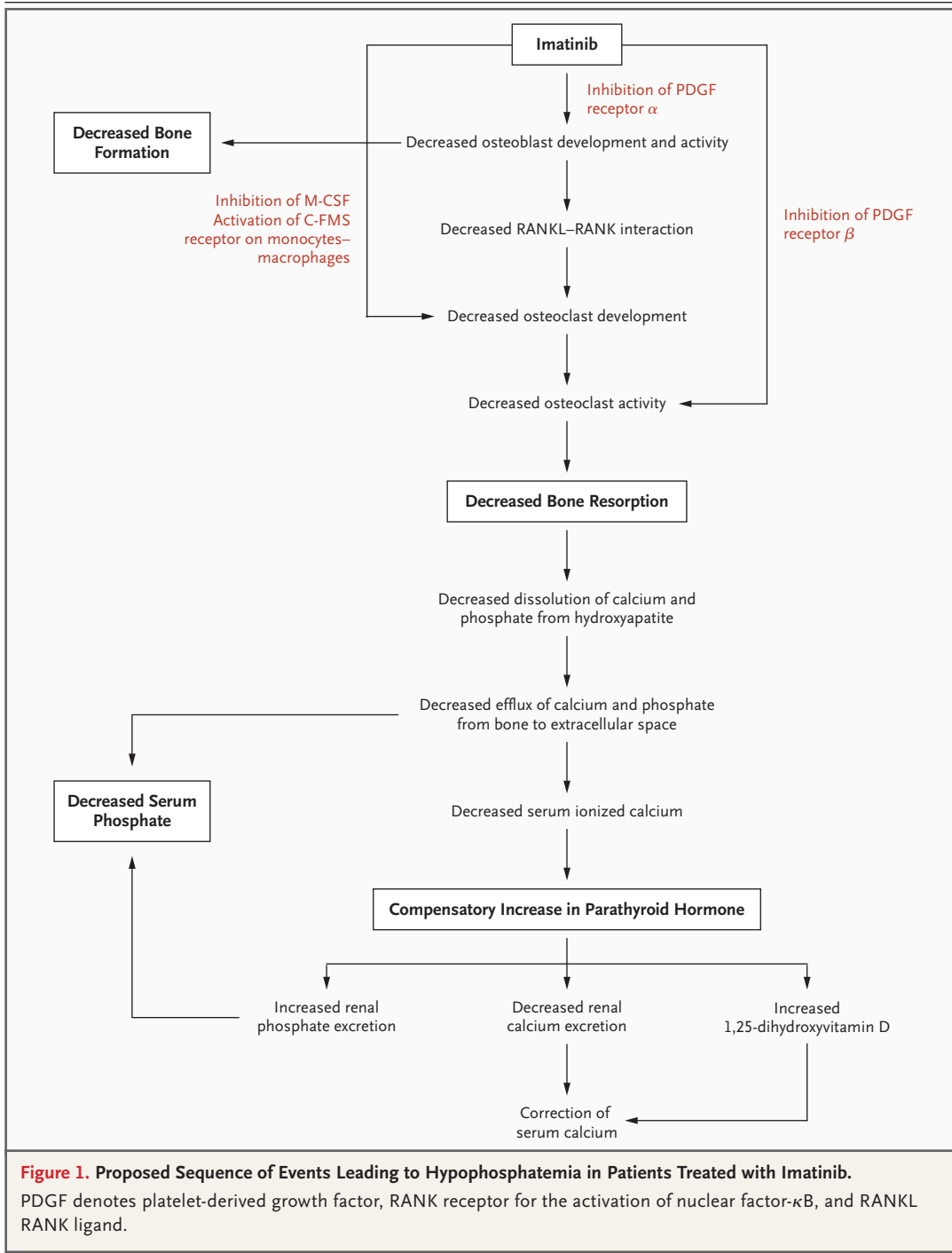
Our study was limited by both the number of patients studied and the timing of the blood and urine sampling. Serum phosphate was not measured in a fasting state because imatinib is typically taken after breakfast, and this schedule was not altered. Despite this fact, hypophosphatemia was observed in the postprandial state, in which dietary phosphate intake would be expected to increase serum phosphate levels. Serum levels of PTH, osteocalcin, and N-telopeptide of collagen cross-links have diurnal variations, with a peak in the early morning, between 3 a.m. and 5 a.m.; PTH levels also have a second peak at 5 p.m.⁸⁻¹⁰ Levels of both osteocalcin and N-telopeptide of collagen cross-links have nadirs in the afternoon and evening (between noon and 8 p.m.), whereas PTH levels have two nadirs — at 10 a.m. and 9 p.m. — that follow the two peaks.⁸⁻¹⁰ In this study, the majority of the blood and urine samples were taken between 9 a.m. and noon. Even though this period is near the time of the first PTH nadir (approximately 10 a.m.), PTH levels were high in the low-phosphate group. This finding strongly suggests that parathyroid function is in fact abnormal in this group.

The results of the correlation analysis (Table 2), which was limited by a small sample size, suggest that hypophosphatemia is associated with decreased levels of calcium, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D. Some degree of accelerated vitamin D metabolism, similar to that seen with phenytoin therapy,¹¹ may account for this finding. However, among the 16 patients with hypophosphatemia, 6 with elevated PTH levels had 25-hydroxyvitamin D levels well within the normal range (greater than 25 ng per milliliter¹²) (see the Supplementary Appendix).

The pattern of disordered metabolism in our

Table 2. Results of Correlation Analysis in Patients with Hypophosphatemia.

Electrolyte Pair in Serum	Correlation Coefficient	P Value
PO ₄ and calcium	+0.63	0.009
PO ₄ and PTH	-0.43	0.12
PO ₄ and 25-hydroxyvitamin D	+0.54	0.005
PO ₄ and 1,25-dihydroxyvitamin D	+0.59	0.04
PTH and calcium	-0.22	0.41
PTH and 25-hydroxyvitamin D	+0.11	0.66
PTH and 1,25-dihydroxyvitamin D	-0.17	0.55



patients differs in some respects from what has been reported for natural causes of hypophosphatemia with renal phosphate wasting: increased blood levels of fibroblast growth factor 23,¹³ low levels of 1,25-dihydroxyvitamin D,¹⁴ and usually, normal levels of PTH.¹³ In our patients with hypophosphatemia, 1,25-dihydroxyvitamin D

levels were in the upper normal range and PTH levels were elevated (see the Supplementary Appendix).

The serum markers of bone metabolism in our patients treated with imatinib suggest that the drug may affect bone-cell activity directly. One possible explanation for the abnormalities in

bone and mineral metabolism seen in these patients is that imatinib, by inhibiting the PDGF receptor, affects the formation and resorption of bone. The expression of the PDGF receptor α gene has been observed in cultured osteoprogenitors and osteoblasts from fetal rats,¹⁵ and the PDGF isoforms PDGF-AA and PDGF-BB have been shown to stimulate replication¹⁶ and migration¹⁷ of rat osteoblasts in vitro. PDGF-BB has been shown to increase the number of rat osteoblasts in vivo,¹⁸ and the survival of osteoblasts may be stimulated by PDGF-BB by way of AKT (protein kinase B) in human and murine cells.¹⁹ PDGF receptor α also plays a critical role in the development of the rat skeleton, as has been demonstrated in rats with mutations of the PDGF receptor α gene.¹⁵

In humans, mature osteoclasts are derived from the monocyte–macrophage lineage.²⁰ The activities of osteoblasts and osteoclasts are tightly coupled because of the interaction of the receptor for the activation of nuclear factor- κ B (RANK) ligand on osteoblasts and its receptor, RANK, on osteoclast precursors.²⁰ The maturation of macrophages into osteoclasts also requires the presence of macrophage colony-stimulating factor (M-CSF), which is secreted by stromal cells and osteoblasts and binds to the colony-stimulating factor 1 receptor (C-FMS) on macrophages.²¹ Imatinib has been shown to inhibit the development of the monocyte–macrophage lineage from normal human bone marrow progenitors in vitro by inhibiting the activation of C-FMS by M-CSF.²² Although the data are limited, there is some evidence that PDGF-BB stimulates bone resorption by osteoclasts in humans directly through PDGF receptor β .²³ Imatinib may therefore interfere with osteoclast function directly by inhibiting PDGF receptor β on osteoclasts, indirectly by inhibiting PDGF receptor α on osteoblasts, or indirectly by inhibiting the activation of C-FMS by M-CSF. On the basis of these data, we propose a model (Fig. 1) that may ex-

plain the abnormalities in bone and mineral metabolism observed in some patients treated with imatinib.

Inhibition of the PDGF receptor may also explain why some patients with either CML or hypereosinophilia had a decrease in plasma lipid levels shortly after starting imatinib. Gottardi et al.²⁴ reported that eight of nine patients had a rapid reduction in cholesterol levels and three of four patients had a decrease in triglyceride levels. Since PDGF binds and phosphorylates the low-density lipoprotein (LDL) receptor–related protein, a member of the LDL receptor superfamily,²⁵ the authors postulate that inhibition of the PDGF receptor may modify the metabolism of lipids.

Hypophosphatemia has also been observed in patients with renal cancer taking sunitinib (Motzer R: personal communication). This observation suggests that abnormalities in bone metabolism may be a feature common to tyrosine kinases that inhibit the PDGF receptor.

In summary, although imatinib inhibits tyrosine kinases associated with specific diseases, our data suggest that in vivo inhibition of the PDGF receptor may also occur and may have clinical consequences. If this is confirmed, routine monitoring of serum phosphate and vitamin D during imatinib therapy may be advisable so that prompt phosphate replacement can be initiated. Chronic, untreated hypophosphatemia can result in impaired bone mineralization, rickets, and osteomalacia. Further study in this area is important, since other tyrosine kinase inhibitors that act on the PDGF receptor are now in clinical use in patients with renal adenocarcinoma and other forms of cancer.²⁶

Dr. Sauter was on the staff of Memorial Sloan-Kettering Cancer Center at the time the research was conducted; he subsequently became an employee of Novartis. Dr. Maki reports having received lecture fees from Novartis. No other potential conflict of interest relevant to this article was reported.

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