Hypophosphatemia and Phosphorus Depletion in Respiratory and Peripheral Muscles of Patients With Respiratory Failure due to COPD*

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In 22 patients (19 men, 3 women; mean [± SD] age, 63 ± 6 years) with chronic obstructive pulmonary disease (COPD), phosphorus content was measured by spectrophotometric methods on muscle fragments of both peripheral (quadriceps femoris needle biopsy in 22 patients) and respiratory muscles (external intercostal muscle surgical biopsy in 14 patients). Thirty age- and sex-matched subjects were used as controls (19 for quadriceps femoris muscle biopsy and 11 for intercostal muscle biopsy). Serum phosphorus levels, as well as the main determinants of overall phosphorus metabolism (dietary intake of phosphorus and renal phosphate handling), were also obtained in all patients and control subjects. Muscle phosphorus content of both respiratory and peripheral muscles was significantly reduced in the COPD patient group, no matter what reference index was used (fat-free dry muscle weight or muscle fragment DNA content); muscle phosphorus depletion was present in about 50 percent of patients with COPD. In the same patient group, a significant relationship between muscle and serum phosphorus levels was demonstrable in the case of peripheral muscles only. No relationship was found between phosphorus content of both types of skeletal muscles and dietary phosphorus intake levels or with nutritional status, even though patients with COPD had significantly reduced anthropometric, biochemical, and immunologic indices as compared with controls. Renal phosphorus handling indices of the COPD patient group were compatible with a condition of inadequacy of the renal compensatory mechanism to hypophosphatemia and phosphorus depletion (low percent tubular reabsorption of phosphorus, low renal threshold concentration values). Our study suggests that phosphorus depletion occurs frequently in COPD, but in this clinical condition serum phosphorus levels are not representative of cellular phosphorus levels. Phosphorus depletion, which is equally severe in respiratory and peripheral muscles, could depend, at least in part, on malnutrition and a condition of renal phosphorus wasting possibly linked to some drugs commonly used in patients with COPD (xanthine derivatives, diuretics, etc).

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FFDM=fat-free dry muscle weight; percent TRP=percent renal tubular reabsorption of phosphate; TmPO4/
GFR=renal phosphate threshold concentration

Hypophosphatemia is a common finding among hospitalized patients: a prevalence of 2 to 5 percent has been reported, 1,2 which increases to 20 to 40 percent if predisposing conditions such as alcoholism, diabetic ketoacidosis, recovery from burns, or sepsis are present.3,4

Hypophosphatemia is also frequently found in the course of respiratory illness: low serum phosphorus values (less than 2.5 mg/dl) have been demonstrated in 25 percent of patients with respiratory illness,4 with a 5 percent prevalence of severely reduced serum levels (less than 1.0 mg/dl);5 in one study, hypophosphatemia was found in 34 of 158 patients with COPD (21.5 percent), with no difference be-

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between patient groups presenting increased severity of respiratory illness.6

Clinical features of hypophosphatemia and phosphorus depletion are protean, as they include neurologic and neuromuscular abnormalities, rhabdomyolysis, erythrocyte dysfunction and hemolysis, leukocyte and platelet dysfunction, hepatic enzyme alterations, and myocardial function derangements.7,8 Phosphorus, in fact, is critical to several processes controlling cell energy production, transport, and utilization.7

Even though negative effects of hypophosphatemia on cells are thought to occur mainly through a decrease of cell phosphorus content,7,9 the relationships between serum and muscle phosphorus levels are not well defined, in particular in patients with respiratory illness. Low phosphorus content has recently been observed in peripheral muscles of patients with COPD with respiratory failure,6 but no data are currently available concerning respiratory muscle phosphorus content in this clinical condition.
The present investigation was thus undertaken to measure muscle phosphorus content in skeletal muscles of patients with COPD: this was carried out by means of surgical biopsy specimens taken from the external intercostal muscles, and needle biopsy specimens from the quadriceps femoris muscle of the same patients. Moreover, the relationship between skeletal muscle phosphorus and serum phosphorus levels was analyzed to define the specificity and sensitivity of hypophosphatemia in predicting muscle phosphorus depletion in the course of COPD.

Methods

Patients

Twenty-two patients (19 male, 3 female; mean [± SD] age, 63 ± 6 years; range, 50 to 78 years) with hypercapnic-hypoxicemic COPD (PaCO₂ 57 ± 9 mm Hg; PaO₂ 47 ± 8) were studied in a pulmonary medicine ward. Patients were selected only if COPD was the primary diagnosis. A diagnosis of COPD had been made during previous hospitalizations or clinic visits and was based on positive history, clinical, and radiologic criteria and standard measurements of pulmonary mechanics (FEV₁ and FEV₁/FVC ratio less than 70 percent of predicted standard). No patient was in a new acute phase of his or her disease or had impaired consciousness. No patient had sepsis or was receiving antacids, phosphorus supplementation, or parenteral nutrition. At the time of the study, most patients were receiving active treatment with one or more of the following drugs, in different combinations and with different regimens: xantine derivatives (20/21), β₂-adrennergic bronchodilators (5/21), oral corticosteroids (6/21), and loop diuretics (8/21). Serum creatinine levels ranged from 0.7 to 1.2 mg/dl.

Experimental Procedure

Muscle biopsy specimens and blood samples were taken after a 12- to 14-h overnight fast. Quadriceps femoris muscle needle biopsy specimens were obtained in all patients: in 14 of the same patients, surgical biopsy specimens from the external intercostal muscles were also performed by a thoracic surgeon. A total of 30 age- and sex-matched subjects served as controls for the muscle biopsy study; they were selected only if they had actual body weight between 95 and 105 percent of ideal body weight, and normal values of body mass index (between 20 and 25), serum albumin (>3.5 g/dl), serum transferrin (>250 mg/dl), total lymphocyte count (>1,800 mm³), arterial blood gases (PaCO₂ <40 mm Hg with PaO₂ > 80 mm Hg), and spirometry (FEV₁ and FEV₁/FVC above 90 percent of the predicted value). Of the control subjects, 19 were medical patients (16 male, 3 female; mean age, 60 ± 6 years; range, 47 to 71 years), hospitalized in a medical ward for benign medical problems (prostatic hypertrophy, urolithiasis, microhematuria, etc); like patients with COPD, they underwent quadriceps femoris muscle needle biopsy under local anesthesia with 2 percent lidocaine. The other control subjects were 11 surgical patients (9 male, 2 female; mean age, 59 ± 9 years; range, 45 to 78 years), hospitalized in a surgical ward for problems with no effects on nutritional status, and requiring elective surgery (cholecystectomy, inguinal hernia, benign mammary nodule ablation, etc); they underwent external intercostal muscle surgical biopsies after 10 to 15 min from anesthesia induction. No statistically significant differences were found between the two subgroups of control subjects with regard to sex, age, nutritional status, arterial blood gases, and spirometry.

In control subjects and patients with COPD, arterial blood gases, urinary and serum electrolytes and creatinine, dietary phosphorus intake, and the main renal phosphate handling parameters (percent tubular reabsorption of phosphate [percent TRP], renal phosphate threshold concentration [TmP0₄/GFR]) were obtained in the 3 days preceding the study. Nutritional status was evaluated in each control subject and patient with COPD before the biopsy, by measuring body weight, (expressed as percent of ideal body weight), body mass index, serum albumin, transferrin, and total lymphocyte count. All subjects were informed of the nature and the possible risks of the study; written consent was obtained from each participant. The protocol of the study was approved by the institutional review board for human studies.

Methods

Arterial pH, PaCO₂, PaO₂, serum albumin, total lymphocyte count, transferrin, serum and urinary phosphorus, and creatinine levels were measured by routine analytical methods, as previously described. Muscle specimens (weight range, 50 to 120 mg) were obtained from the lateral portion of the quadriceps femoris, by the Bergstrom needle biopsy technique, with a 6-mm-diameter needle, as previously described. Surgical biopsy specimens from the external intercostal muscles were taken from the fifth intercostal space on the anterior axillary line (fragment weight range, 46 to 115 mg). Fragments of both types of muscle were rapidly frozen and stored in liquid nitrogen. They were then freeze dried, extracted in petroleum ether, and muscle powder was obtained after separation of connective tissue.

Total muscle phosphorus content was obtained after acid extraction of muscle powder according to the method of Chen et al as applied by Montanari et al; the method is based on the formation of a phosphomolybdate complex subsequently reduced by ascorbic acid and read at 820 nm with a spectrophotometer (model DU 65 Beckman, Beckman Instruments, Inc, Fullerton, Calif). Muscle electrolyte content was expressed both as millimoles per kilogram of fat-free dry muscle weight (mmols/kg of FFDM, i.e. weight of muscle powder after freeze drying and petroleum ether extraction), and as millimoles per gram of muscle DNA content (mmols/g DNA). In the case of patients with COPD, only those with double biopsies (14 of 22) had muscle DNA content measured on both quadriceps femoris and external intercostal muscle fragments.

An estimate of dietary intake of phosphorus was obtained on the basis of a 3-day dietary record as previously described, as standard values the 1980 Recommended Dietary Allowances (RDA) for phosphorus in adults with more than 51 years (800 mg/d) were utilized. Body mass index was calculated on the basis of height and weight. Renal phosphorus excretion was evaluated on the basis of two indices of renal phosphorus handling: the urinary phosphorus/urinary creatinine ratio (mg/kg), the percent tubular reabsorption of phosphate (calculated as percent TRP = 1 - [Pu/XCrs]/[PsXCru]), where Pu is urinary phosphorus concentration in mg/dl, Crs is serum creatinine level in mg/dl, Ps is serum phosphorus in mg/dl, Cru is urinary creatinine concentration in mg/dl, and the renal phosphate threshold concentration (TmP0₄/GFR) in mg/dl, obtained from percent TRP and Ps by the nomogram of Walton and Bijovet.

Statistics

Data were expressed as arithmetic mean ± SD. Statistical analysis was performed using the two-tailed Student’s t test for independent samples. Standard regression and correlation statistics by the least-square method was applied. Statistical significance was defined as a probability of type 1 error of less than 0.05. Personal computer packages (Excel, Microsoft Corp, Redmond, Wash, and Statpak, Northwest Analytical, Portland, Ore) were used for data storage, calculations, and statistics.
Table 1—Serum and Muscle (Respiratory and Peripheral Skeletal Muscles) Phosphorus Levels in Control Subjects and Patients With COPD

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects</th>
<th>Control Subjects</th>
<th>Patients With COPD</th>
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<tbody>
<tr>
<td>(External Intercostal</td>
<td>(Quadriceps Femoris</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle Biopsy)</td>
<td>Muscle Biopsy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=11</td>
<td>n=19</td>
<td>n=22</td>
<td></td>
</tr>
<tr>
<td>Serum phosphorus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mg/dl</td>
<td>3.64 ± 0.33</td>
<td>2.96 ± 0.77*</td>
<td></td>
</tr>
<tr>
<td>mmol/L</td>
<td>1.17 ± 0.11</td>
<td>0.96 ± 0.25*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n=30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>External intercostal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>phosphorus content</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mmol/kg FFDM</td>
<td>335 ± 21</td>
<td>260 ± 27*</td>
<td></td>
</tr>
<tr>
<td>mmol/g DNA</td>
<td>156 ± 20</td>
<td>98 ± 29*</td>
<td></td>
</tr>
<tr>
<td>Quadriceps femoris</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>phosphorus content</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mmol/kg FFDM</td>
<td>319 ± 25</td>
<td>281 ± 34*</td>
<td></td>
</tr>
<tr>
<td>mmol/g DNA</td>
<td>115 ± 10</td>
<td>87 ± 21*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n=14)</td>
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*p < 0.001 as compared with the respective control group (Student’s t test).

RESULTS

Mean serum phosphorus levels of the COPD patient group were significantly reduced as compared with those of control subjects (Table 1); 6 of 22 patients with COPD had phosphorus values less than 2.5 mg/dl. Phosphorus content of both quadriceps femoris and external intercostal muscles of patients with COPD was significantly reduced as compared with the respective control subject group, regardless of the reference base for muscle phosphorus (FFDM or DNA) (Table 1). A significant correlation was found in the COPD group between the two types of skeletal muscles (Fig 1). In the same patients, a statistically significant relationship was found between serum phosphorus and quadriceps femoris muscle phosphorus content, whatever the reference base used, i.e., DNA (r = 0.754, n=14, p<0.01) (Fig 2) or FFDM (r = 0.711, n=22, p<0.001), but not between serum phosphorus and external intercostal muscle phosphorus (Fig 3). No statistically significant relationship was found between quadriceps femoris or intercostal muscle phosphorus content and serum

**Pmi mmoles/Kg DNA**

![Graph showing the relationship between Pmi and Pmq](https://via.placeholder.com/82x78)

**Pmq mmoles/g DNA**

![Graph showing the relationship between Pmq and Pm](https://via.placeholder.com/82x78)

**FIGURE 1.** The relationship between external intercostal muscle phosphorus (Pmi) and quadriceps femoris muscle phosphorus (Pmq) contents in the COPD patient group is shown. As a reference index for muscle phosphorus content values, muscle DNA content was used.

**FIGURE 2.** The relationship between quadriceps femoris muscle phosphorus content (Pmq), expressed as millimoles of phosphorus per gram of muscle DNA content, and serum phosphorus levels (Ps) in the COPD patient group is shown.
Figure 3. The relationship between external intercostal muscle phosphorus content (Pmi), expressed as millimoles of phosphorus per gram of muscle DNA content, and serum phosphorus levels (Ps) in the COPD patient group is shown.

phosphorus values, no matter the reference base (quadriceps femoris muscle: \( r = -0.26, p = 0.19, p = \text{NS} \) by using FFDM; \( r = -0.0032, n = 11, p = \text{NS} \) by using FFDM; \( r = 0.100, n = 11, p = \text{NS} \) by using DNA). No correlation was found between arterial blood gas values and phosphorus content of either type of skeletal muscle in patients with COPD. Dietary phosphorus intake of the COPD patient group was not statistically different from that of controls (Table 2), and it was above RDA in all patients with COPD except four. No relationship was found between dietary phosphorus intake and phosphorus content of either quadriceps femoris or external intercostal muscles. In the COPD patient group, urinary phosphorus handling was impaired, since both percent TRP and TmPO₄/GFR were significantly reduced as compared with control values (Table 2). Nutritional indices of patients with COPD were significantly lower than those of control subjects (Table 3).

**DISCUSSION**

The present study demonstrates that patients with COPD manifest important alterations of skeletal muscle phosphorus content, and that muscle phosphorus depletion is not easily detected on the basis of serum phosphorus values: phosphorus content in both respiratory (external intercostal) and peripheral skeletal muscles (quadriceps femoris) was in fact significantly reduced as compared with control subject values, but the sensitivity and specificity of serum phosphorus values were low. Our results thus confirm and extend those obtained in a previous study on the quadriceps femoris muscle phosphorus content of patients with COPD.⁶

Even though most body phosphorus is found in the bone, skeletal muscle represents about 40 percent of cell body mass, and can be considered as tissue representative of cell body mass stores of phosphorus; thus, our results are consistent with the presence of a condition of true cell phosphorus depletion in the patients studied. Moreover, phosphate depletion

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**Table 2—Dietary Intake and Renal Excretion of Phosphorus in Control Subjects and Patients With COPD**

<table>
<thead>
<tr>
<th></th>
<th>Control Group (n=30)</th>
<th>Patients With COPD (n=22)</th>
<th>Unpaired Data Student's t Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphorus intake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mg/24 h</td>
<td>1.021 ± 1.48</td>
<td>936 ± 178</td>
<td>NS</td>
</tr>
<tr>
<td>mmol/24 h</td>
<td>32.9 ± 4.7</td>
<td>30.2 ± 5.6</td>
<td></td>
</tr>
<tr>
<td>Percent renal tubular reabsorption of phosphorus</td>
<td>88.3 ± 5.1</td>
<td>84.8 ± 6.6</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Renal phosphate threshold concentration, mg/dl</td>
<td>3.61 ± 0.44</td>
<td>2.73 ± 0.93</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 3—Nutritional Indexes of Control Subjects and Patients With COPD**

<table>
<thead>
<tr>
<th></th>
<th>Control Group (n=30)</th>
<th>Patients With COPD (n=22)</th>
<th>Unpaired Data Student's t Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual body weight, kg</td>
<td>68.7 ± 7.0</td>
<td>61.3 ± 9.7</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Body weight, % of ideal body weight</td>
<td>100.7 ± 3.9</td>
<td>82.5 ± 12.3</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>23.4 ± 1.7</td>
<td>22.1 ± 2.9</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Albumin, g/dl</td>
<td>3.9 ± 0.3</td>
<td>3.4 ± 0.7</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Transferrin, mg/dl</td>
<td>306 ± 31</td>
<td>231 ± 61</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Lymphocytes, mm³</td>
<td>2.071 ± 214</td>
<td>1.791 ± 401</td>
<td>p&lt;0.01</td>
</tr>
</tbody>
</table>
seems not to spare skeletal muscle tissue throughout the body, for our study demonstrated that muscle total phosphorus content was reduced in both respiratory and nonrespiratory skeletal muscles of patients with severe COPD.

No correlation was found in our study between serum phosphorus levels and respiratory muscle phosphorus content, while serum phosphorus was significantly related to quadriiceps femoris muscle phosphorus. In the latter case, too, hypophosphatemia seemed to be a poor predictor of phosphorus depletion in patients with COPD, since two of six patients with serum phosphorus values lower than 2.5 mg/dl had muscle phosphorus content values in the normal range (with 2 SDs from control group mean). In the case of respiratory muscle phosphorus, this relationship was lacking despite the absence of several factors able to influence transmembrane redistribution between extracellular and intracellular compartments, ie, parenteral nutrition, acute acid-base disorders, and mechanical ventilation. 3.9 It is worth mentioning that the relationship between extracellular phosphorus and muscle phosphorus content is not only dependent on transcellular shifting, but also on cell condition before hypophosphatemia, as well on the balance between tissue metabolic needs and overall phosphorus homeostasis. For example, experimental phosphorus depletion, while not easily achievable in adult animals or in nongrowing subjects, can be demonstrated after 1 to 3 days in young subjects and in acutely anabolic patients (nutritional recovery syndrome, burn patients, etc). 8,19

We cannot exclude the possibility of a limitation resulting from our methodology, which measures total phosphorus content of the muscle (ie, organic plus inorganic phosphorus); the true level of cell inorganic phosphorus is difficult to estimate, and different analytical methods give various results. 20-23 The variation being due to the fact that phosphorus fractions other than true inorganic phosphorus are included in the determinations, because of the decomposition of organic phosphate compound. However, total muscle phosphorus seems to be a reliable index of the overall skeletal muscle cell phosphorus pool, and the results obtained in our control subjects are similar to those obtained by other authors. 15,21 The possibility that low muscle phosphorus values in patients with COPD can be linked to the presence of contaminants was excluded in our study, as the finding of reduced phosphorus content values in the two types of skeletal muscle studied was confirmed, regardless of the reference index, ie, either fat-free dry muscle weight or DNA content. DNA has been advocated as a reference index for muscle composition studies on the grounds that it represents a reliable parameter of the number of cells in the muscle fragment studied, and is thus less affected, vs the commonly used FFDM, by cell size decrease or by an increase in fragment connective tissue. 24 The use of DNA in particular allowed us to exclude the possibility of falsely low phosphorus content values due to alterations in muscle fragment connective content.

Our results indicate that serum phosphorus levels are not highly predictive of total muscle phosphorus content, although muscle phosphorus is likely to be reduced in patients with COPD if severe hypophosphatemia is present. Moreover, our study provided some insight into the pathogenesis of phosphorus metabolism derangements; in fact, we examined some possible determinants of phosphorus metabolism, and in particular of cell phosphorus content, ie, dietary intake, renal phosphate handling, and nutritional status.

Although intermediary mechanisms, including phosphorus exchange between the extracellular fluid and the skeleton or soft tissues, could play an important role in overall phosphorus metabolism, the fundamental process of phosphorus homeostasis integrates intestinal absorption and renal excretion. 8,9 In our patients with COPD, we cannot exclude previous dietary phosphorus deficits or the possibility of alterations in its intestinal absorption, but the higher than RDA intake of phosphorus in most patients (18 of 22 patients), suggests that a selective deficiency of phosphorus is not the main cause of hypophosphatemia and phosphorus depletion in this case. Although nutrient intake evaluation by food records implies a certain degree of unreliability and provides adequate information only on nutrient intake during the period considered, in the case of phosphorus, the 3-day dietary record method has been demonstrated to underestimate dietary phosphorus intake by 15 to 25 percent. 25 Moreover, these results are in keeping with those obtained in a group of 158 patients with COPD with similar characteristics in whom dietary phosphorus intake has recently been evaluated. 6

Important alterations of renal phosphate handling were also found in the patients with COPD studied: increased renal phosphorus excretion with a reduced renal tubular reabsorption of phosphorus and renal phosphorus threshold concentration (TmPO4/GFR) values were demonstrated. In particular, TmPO4/GFR—ie, the ideal concentration of phosphate above which most of the phosphorus filtered by the renal glomerulus is found in urine—is one of the parameters that best characterizes renal phosphate handling. 26 Physiologic renal response to hypophosphatemia and phosphorus depletion normally involves an adaptive increase in TmPO4/GFR (ie, a condition of renal phosphorus sparing); thus, by assessing this index in patients with COPD, the contribution of a renal mechanism to the pathogenesis of
phosphorus depletion can be determined. A condition of inappropriate phosphaturia was present in our patients with COPD, as the association of reduced TmPO₄/GFR levels and low serum phosphorus levels suggests the presence of factors inappropriately reducing renal phosphate reabsorption, even at low levels of filtered phosphate load. Factors interfering with the renal homeostatic response to hypophosphatemia in patients with COPD have recently been addressed. In the course of COPD, the prevalence of both low serum phosphorus and TmPO₄/GFR values was higher among the patients taking one or more drugs commonly used in this kind of respiratory disease and demonstrated as negatively affecting renal phosphate handling: xanthine derivatives, corticosteroids, loop diuretics, and β-2-adrenergic bronchodilators. Moreover, the administration of therapeutic doses of each of these drugs in patients with COPD previously not taking any drug was associated with a reduction of TmPO₄/GFR values. In the patients with COPD considered herein, TmPO₄/GFR was reduced in 9 of 22 patients, and most of the patients were taking one or more of the above drugs. As in a previous study on a wider population of patients with COPD, in this case too, chronic renal phosphate leakage could represent a likely mechanism of phosphorus depletion.

The evaluation of nutritional status of the COPD patient group indicates a condition of malnutrition: anthropometric, biochemical, and immunologic indices were, in fact, significantly decreased as compared to those of control subjects. Low muscle phosphorus content has been demonstrated in malnourished subjects. Thus, also malnutrition, which is a common finding among patients with COPD, as reported in the literature, may have contributed to muscle phosphorus content derangement found in our patients.

The clinical relevance of our data derives from the fact that phosphorus metabolism derangements have been indicated as possible determinants of respiratory muscle weakness. Even though in our study respiratory muscle performance was not assessed, significant alterations of respiratory muscle function have been demonstrated in the course of experimentally induced phosphorus depletion and after acute changes of serum phosphorus in man. Moreover, respiratory muscle weakness, which improved after phosphorus supplementation, was associated with low levels of the anion in the extracellular fluid. Molecular mechanisms mediating skeletal muscle myopathy of phosphorus depletion at the cellular level have been reviewed recently. Abnormalities were found in the creatine phosphate shuttle, in mitochondrial oxidative phosphorylation, and in myofibrillar energy utilization. Under experimental conditions, these events were preceded by a marked reduction of cellular phosphorus stores. In spite of the fact that markedly reduced levels of ATP and phosphocreatine have been observed in limb muscles of patients with COPD the extent to which phosphorus depletion and/or hypophosphatemia are responsible for both muscle energy metabolism alterations and muscle functional impairment is not well defined. In a report on a patient with hypophosphatemic respiratory failure, however, prolonged abnormalities of cell energy metabolism in the forearm muscle were demonstrated by phosphorus nuclear magnetic resonance spectroscopy, in spite of prompt correction of reduced phosphorus levels. In the case of patients with respiratory illness such as patients with COPD, hypophosphatemia and phosphorus depletion could represent the central point of a vicious circle, as these alterations, which are probably the consequence of many factors related to chronic respiratory illness (respiratory function alterations, undernutrition, drugs, etc), could in turn render respiratory failure even more severe, by negatively influencing respiratory muscle function. Further studies aimed at correlating both muscle phosphorus content alterations with respiratory muscle function measurements are thus required.

Intensive treatment of hypophosphatemia in patients with respiratory illness remains controversial, inasmuch as carefully controlled studies have not yet been performed. Hypophosphatemia is thought to produce a clinically relevant phosphate depletion syndrome when it occurs in an individual who is already debilitated by acute or chronic illness; that is, the metabolic changes have more impact upon the "sick" cells, on which phosphorus depletion is superimposed. Patients with an underlying disease, and at risk for phosphate depletion syndrome, include subjects with malabsorption, malnutrition, cancer, chronic alcoholism, recovering from severe burns, and probably patients with COPD as well.

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