14. Phosphorus Depletion in Limb and Respiratory Muscles of Patients with Chronic Obstructive Pulmonary Disease (COPD): A Preliminary Report

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Introduction

Phosphorus plays a key role in cellular biochemical reactions responsible for energy production, storage, and utilization and represents a major component of membranes and other cell structures: thus, the maintenance of normal phosphorus balance and both normal serum and cellular phosphorus levels is critical for the normal function of the organism.[1,2] In both experimental and clinical conditions hypophosphatemia and phosphorus depletion are associated with a wide spectrum of clinical syndromes such as myocardial failure, hepatocellular damage, hemolysis, platelet and leucocyte disfunction, osteomalacia and spontaneous fractures, hypoparathyroidism, impaired glucose tolerance, etc.[3] Moreover, neurologic and neuromuscular signs and symptoms such as ataxia, confusion, delirium, tremor, hyporeflexia, skeletal muscle weakness, and rhabdomyolysis have been observed.[1,3] Hypophosphatemia and/or phosphorus depletion have been equally indicated as possible determinants of respiratory muscle weakness in the course of respiratory failure.[4,5] In fact, an impairment of respiratory muscle contractile properties has been demonstrated in the course of hypophosphatemia, which improves with phosphorus repletion.[6,7] Hypophosphatemia is a common finding in the course of respiratory illnesses, with a prevalence of about 25%; in 5% of the same patients serum phosphate (Ps) levels may be extremely low (less than 1 mg% or 0.33 mmol/l).[8,9]

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Recently, in a large series of 90 COPD patients, the prevalence of moderate (Ps < 2.5 mg or 0.83 mmol/l) and severe hypophosphatemia (Ps < 2.0 mg% or 0.66 mmol/l) was found to be respectively 14% and 9%;[10] moreover, in two patients with Ps < 2 mg% who underwent skeletal muscle needle biopsy, muscle phosphorus content (Pm) was reduced if compared to both normophosphatemic COPD patients and healthy control subject values.

No data are currently available concerning respiratory rauscle phosphorus content values in such conditions. The aims of this preliminary study were thus: (a) to evaluate muscle phosphorus content in respiratory muscles and in limb skeletal muscles in a group of patients with COPD and Chronic Respiratory Failure (CRF); (b) to determine the possible relationships between serum and skeletal muscle phosphorus in the same patients.

Patients and Methods

Thirteen patients (11M, 2 F, mean age 66 yrs ± 7 SD) with COPD and CRF ($PaCO_2$ 61 mmHg ± 8 SD; PaO_2 44 ± 7 SD) were studied. They were selected only if COPD was the primary diagnosis. COPD diagnosis had been made during previous hospitalizations or clinical visits and was based on positive history, clinical and radiological criteria, and standard measurements of pulmonary mechanics (FEV_1 values and FEV_1/FVC ratio less than 70% of predicted standards). No patient had impaired consciousness or was on parenteral nutrition. At the time of the study most patients were on active treatment with differently scheduled xanthine-derivatives, corticosteroids, diuretics and digitalis. No patient was diabetic or was receiving phosphorus supplements or antacids at the time of the study.

Serum creatinine levels ranged from 0.87 to 1.32 mg/dl. All patients underwent needle biopsies from the lateral portion of the quadriceps femoris muscle, according to the Bergstrom technique;[11] in five patients surgical biopsies from the external intercostal muscles (5th intercostal space, anterior axillary line) were also performed under local anesthesia.

Muscle samples (weighing 23-72 mg) were rapidly dissected free from visible fat or connective tissue and placed in preweighed quartz tubes; FFS (muscle fat-free solids) were then obtained, as previously described in detail.[12] Muscle fragments were digested with 0.200 ml of 70% $HClO_4$, and muscle total phosphorus content (Pm) was measured by the Chen method[13] and expressed as mmol/kg of FFS.

A group of twelve age-and sex-matched healthy subjects were utilized as controls for the quadriceps femoris study; external intercostal muscle surgical biopsies were obtained at anesthesia induction in another group of eleven subjects, with normal respiratory function, undergoing elective surgery. Serum phosphorus (Ps) was also measured in all patients and control subjects. All subjects and/or their next of kin were informed of the nature and the possible

risks of the study, and consent was obtained from each participant and/or his or her relatives.

Statistics

Data are presented as mean ± SD. Student's "t" test for unpaired data was used to assess the significance of the differences between the means: standard techniques of linear regression and correlation by the least squares method were utilized. A statistical package (Statpak, Northwest Analytical Inc., Portland, OR) was used for calculations.

Results

Mean serum phosphorus levels of COPD patients were not significantly different from control values. Phosphorus content of both quadriceps femoris and external intercostal muscles was significantly reduced as compared to control values. (Fig. 1); no correlation was found between P_m values of the two kinds of muscle (Fig. 2). A significant ($r=0.65$, $n=13$, $p<0.05$) direct relationship was found between P_s and

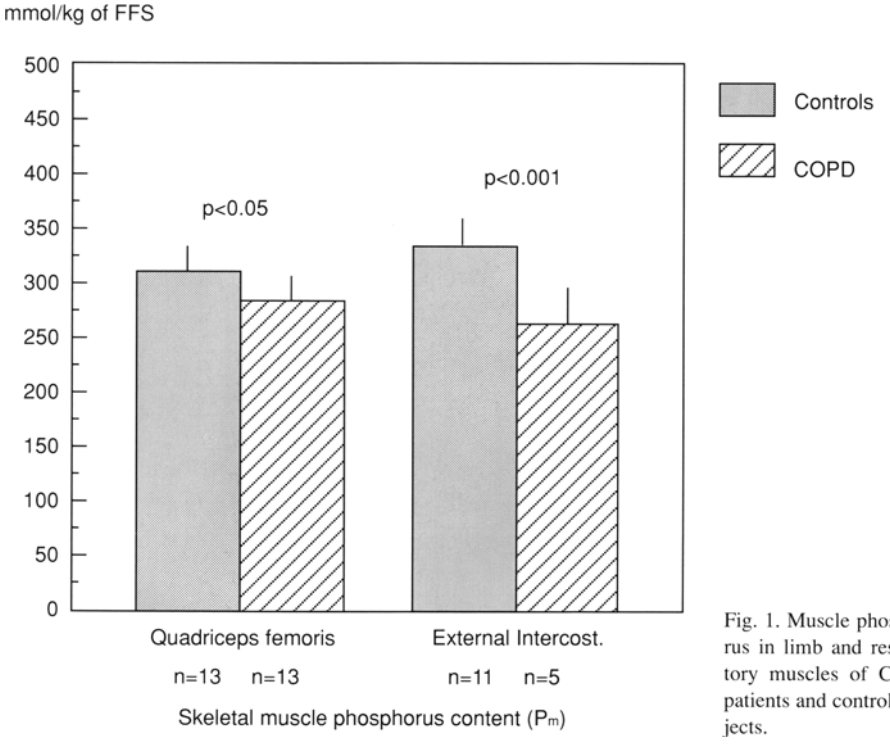

Fig. 1. Muscle phosphorus in limb and respiratory muscles of COPD patients and control subjects.

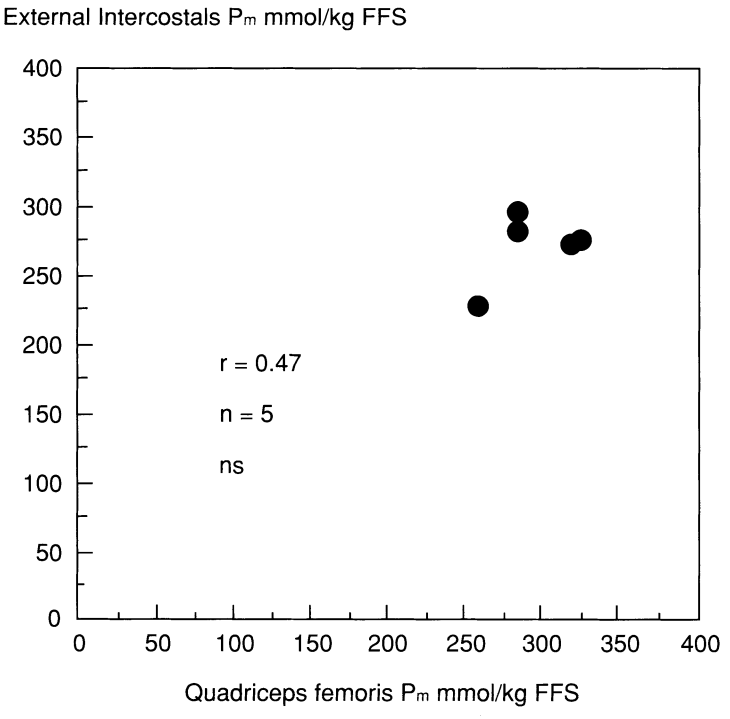

Fig. 2. Relationship between limb and respiratory muscle phosphorus (P_m) in COPD patients.

quadriceps femoris P_m (Fig. 3), but not between P_s and quadriceps femoris P_m (Fig. 3), and not between P_s and external intercostal muscles P_m (Fig. 4). No correlation was found between $PaCO_2$ or PaO_2 and P_m values of either quadriceps femoris or external intercostal muscles in COPD patients.

Discussion

Our preliminary report indicates that muscle phosphorus content may be reduced in both limb and respiratory muscles of patients with severe COPD. This abnormality probably reflects the influence of systemic factors negatively affecting skeletal muscle phosphorus metabolism, since it occurs to a similar extent in both resting limb and active respiratory muscles. Among these factors, nutritional depletion[14] and several drugs (xanthine derivatives, diuretics, corticosteroids, etc.) commonly used in course of COPD, all with a phosphaturic effect,[2,3,15,16] could play an important role.

In our patients, no correlation was found between serum phosphorus levels and respiratory muscle P_m, while hypophosphatemia was significantly related to low P_m content values in the quadriceps femoris muscle: however, in this latter case too, hyphophosphatemia seems to be a poor predictor of phosphorus depletion in COPD

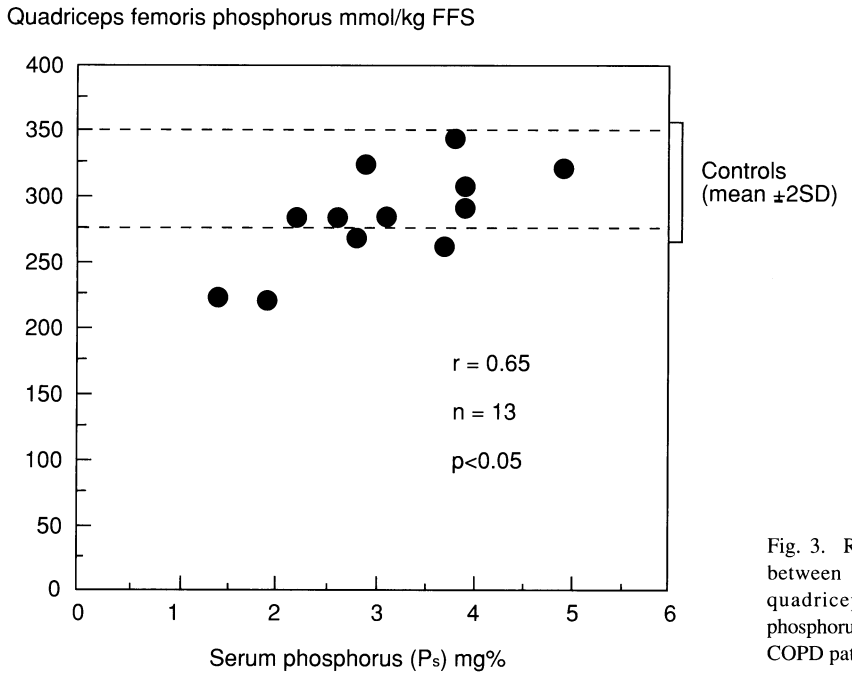

Fig. 3. Relationship between serum and quadriceps muscle phosphorus content in COPD patients.

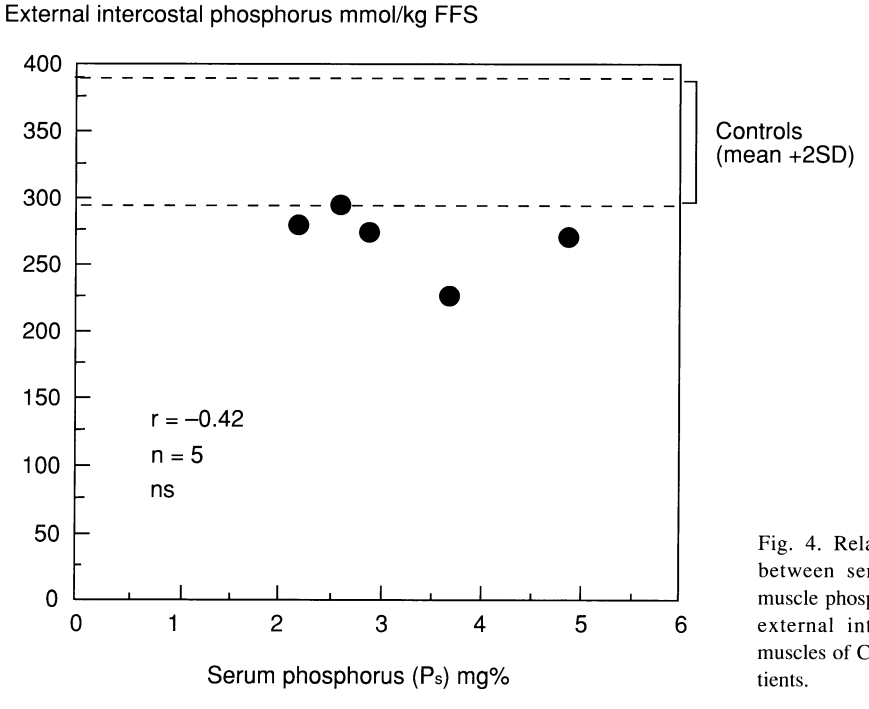

Fig. 4. Relationship between serum and muscle phosphorus in external intercostal muscles of COPD patients.

patients, since two patients of four having P_s values lower than 2.5 mg% showed P_m values in the normal range. Our results thus indicate that serum phosphorus levels are not predictive of muscle phosphorus content, although P_m may be reduced in COPD patients if severe degree hypophosphatemia is present.

Molecular mechanisms mediating the skeletal muscle myopathy of phosphorus depletion at cellular level have been recently discussed.[17] Abnormalities were found in the creatine phosphate energy shuttle required for cellular energy transport, in mitochondrial oxidative phosphorylation, and in myofibrillar energy utilization;[17] also, under experimental conditions, these events were preceded by a marked reduction in cellular phosphorus stores. Actually, in spite of the fact that markedly reduced levels of ATP and phosphocreatine have been observed in limb[18] and respiratory[19] muscles of COPD patients, 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 COPD patients other factors such as intracellular acidosis,[12] magnesium depletion,[20] and malnutrition itself[14,21] may also contribute to the cell energy metabolism alterations demonstrated.

Further studies aimed at correlating both muscle phosphorus content and cell energy metabolism alterations with respiratory muscle function measurements are needed in order to assess the functional and clinical significance of phosphorus metabolism alterations in COPD.

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