Kronik Obstrüktif Akciğer Hastalığında Hipofosfatemi Prevalansı ve Hastalığın Şiddetiyle Serum ve Kas Fosfor Düzeyleri Arasındaki İlişkinin İncelenmesi

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ÖZET
Kilo kaybı ve iskelet kası zayıflığı, KOAH'lı olgularda yaygındır ve KOAH'ın seyrini ve prognozunu etkileyebilir. Hipofosfatemi, sıklıkla kas zayıflığıyla karakterize olup KOAH'lı olgularda sık saptanan bir bulgudur.
Çalışmamızın amacı; farklı şiddette seyreden KOAH'lı olgularda kas ve serumda fosfor düzeyini, prevalansını saptamak ve hastalığın şiddetiyle hipofosfatemi arasındaki korelasyonu belirlemekti.
Çalışmaya 15 KOAH'lı olgu alındı. Hastalığın şiddeti ATS kriterleri gözönüne alınarak FEV_1 değerlerine göre belirlendi.Lokal anestezi ile gastroknemius kasından kesi yapılarak alınan kas numunelerinden muscle fat free dry solids (FFS) hazırlandı. İstatiksel değerlendirmede Pearson korelasyon analizi, Man-Whitney U testi, Fisher's Exact testi kullanıldı.
KOAH'lı olgularda hipofosfatemi (P<2.5mg/dl) prevalansı %20 olarak bulundu. Hipofosfatemisi olan olgularda kas P düzeyleri, serum P düzeyleri normal olan olgulardan daha düşük olarak saptandı. Fakat aradaki fark istatistiksel olarak anlamlı değildi(p>0.05). Olguların %40'ı evre II, %60'ı evre III olarak bulundu. Evre III olgularda serum ve kas P düzeyleri evre II olgulara göre düşük saptandı. İstatistiksel olarak anlamsız olmakla beraber hipofosfatemisi olan olgularda KOAH'ın daha şiddetli seyrettiğini saptadık (p>0.05). Bu da hipofosfateminin, KOAH'lı olgularda gelişen solunum yetmezliğine katkıda bulunabileceğini düşündürmektedir.
Akciğer Arşivi: 2003; 4: 16-20
Anahtar kelimeler: Kronik obstrüktif akciğer hastalığı, serum ve kas fosforu, solunum yetmezliği

SUMMARY
Hypophosphatemia Prevalence in Chronic Obstructive Pulmonary Disease, the Evaluation of the Relationship Between the Severity of the Disease and Phosphorus Content in Serum and Muscle
Weight loss and skeletal muscle weakness are frequently seen in patients with chronic obstructive pulmonary disease (COPD) and they can affect the course and prognosis of COPD. Hypophosphatemia is seen frequently in COPD patients and it is characterized by the muscular weakness. The aim of our study was to evaluate both serum and muscle phosphorus (P) level and hypophosphatemia prevalence among COPD patients and also to determine the relationship between hypophosphatemia and the severity of COPD. Fifteen COPD patients were included to the study. We assessed the severity of the disease in each patient by analyzing the FEV1 levels according to the American Thoracic Society (ATS) criteria. Muscle samples were obtained from gastrocnemius muscle by local anesthesia and from those muscle fat free dry solid (FFS) were prepared. Statistical analysis was performed using Pearson Correlation Analysis, Mann Whitney U test and Fisher's Exact test. The prevalence of hypophosphatemia(P<2.5mg/dl) was found 20 % among COPD patients. We found muscle P content lower in cases with hypophosphatemia than the group with normal serum level,but this correlation was not statistically significant(p>0.05). Forty percentage of cases were in stage II, 60% were in stage III. Patients who were in stage III had lower serum and muscle P content than the group with stage II. Although it was statistically nonsignificant (p>0.05), we found that the course of COPD is severe in cases with hypophosphatemia. These results suggest that hypophosphatemia might be effective in the development of respiratory failure in COPD patients.
Archieves of Pulmonary: 2003; 4: 16-20
Key words: Chronic obstructive pulmonary disease, serum phosphorus,muscle phosphorus,respiratory failure

Introduction

Weight loss and skeletal muscle weakness are frequently seen in COPD patients and they might affect the course and prognosis of the disease. Hypophosphatemia (P<2.5mg/dl) is often characterized by muscle weakness and also it is a common laboratory finding seen in COPD patients (1,2). In these cases high prevalence of hypophosphatemia and defect in renal phosphate reabsorption have been found. The phosphorus

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decrease in respiratory and peripheral muscles might be caused by malnutrition or the use of theophylline, diuretics, corticosteroids and β-adrenergics which increases renal phosphorus excretion (3). Muscle phosphorus may be indicative for the determination of body cell stores as muscle cells represent the 40 % of body cell mass (4). Effect of hypophosphatemia on muscle energy metabolism and muscle dysfunction has not been well understood. Further studies evaluating the relationship between serum and muscle P content and muscle contractile dysfunction are needed to assess the clinical and functional importance of metabolic alteration in COPD patients. In the course of COPD knowledge about hypophosphatemia is limited. Especially, the prevalence, severity and factors causing the electrolyte alteration have not been examined so far (3).In this study our aim was to evaluate the prevalence of hypophosphatemia both in serum and muscle of COPD patients and also to determine the relationship between the severity of the disease and serum and muscle phosphorus level.

Materials and Methods

Fifteen patients with a diagnosis of COPD who were hospitalized between October 2000-January 2001 were included into the study. The study was approved by our scientific ethical committee and all patients gave full informed, written consent. The median age of the patients was 62±15.6 years (range 44-87 years). All of the patients were male. Diagnosis of COPD was suggested by history, physical examination, radiologic criteria and measurement of pulmonary function. Patients having diabetes mellitus, malignancy, renal failure and malnutrition were not included into the study. The severity of COPD was assessed by analyzing FEV_1 level according to the ATS criteria (predicted FEV_1 % ≥50 stageI, 35-49 stageII, < 35 stageIII). Six out of 15 patients were found in stage II, 9 in stage III.

During the study, the selected patients were treated with the following drugs (xanthine derivatives, digitalis, thiazide diuretics,loop diuretics, corticosteroids and β2-agonists). For each patient; spirometry, measurement of arterial blood gases, serum and muscle P content were all performed. Patients rested for 15 minutes before the spirometry and the test was performed by the machine MIR SPİROLAB.

Venous blood samples were obtained on an empty stomach in the morning and the serum phosphorus level was measured. For the measurement 1 Lab 1800 Chemistry analyzer and 1 Lab P test reagent were used and the results were expressed as mg/dl. The normal range of serum P level in our labaratory is 2.5-4.5mg/dl. Levels lower than 2.5mg/dl was considered as hypophosphatemia. Muscle specimens were obtained from the gastrocnemius by means of surgical biopsy technique under the local anesthesia.

Muscle samples were immediately dissected free from visible fat and connective tissue and then muscle fat free dry solids (FFS) were obtained. The samples weighting 44-114 mg were homogenized by 2 mmol, pH:7.4 tris tampon. Later they were santrifuged at 1300 for 5 minutes and phosphorus was studied at supernatant. The results were expressed as mg/kg/FFS.

Statistics

All statistical analyses were performed by the data obtained from 15 patients. SPSS for windows release package program was used. The comparative analysis of serum phosphorus level and muscle phosphorus content with the other variables was performed by using the Pearson Correlation Analysis. Mann Whitney U test was used to compare the group with normal serum phosphorus level and the other group having hypophosphatemia according to the stage of the disease. The correlation between serum phosphorus level and the stage was evaluated by using Fisher's Exact test. A level of $p<0.05$ was accepted statistically significant.

Results

We revealed hypophosphatemia in 3 patients. Hypophosphatemia prevalence was found as 20%. Forty percentage of cases were in stage II, 60% were in stage III. Prevalence of hypophosphatemia and its relationship with the stage of COPD are shown in table I. There was no statistically significant correlation between stage II and

III according to the hypophosphatemia (p>0.05). The relationship between serum-muscle phosphorus level and FEV_1 level one by one were analysed and nonsignificant correlation was found. The distribution of the mean serum-muscle phosphorus values according to hypophosphatemia and normal serum P level is seen in table II. The correlation between serum phosphorus level and muscle phosphorus content is shown in figure I. Muscle P content was found lower in cases with hypophosphatemia than the group with normal serum level. There was no statistically significant correlation between serum phosphorus level and muscle phosphorus content (p>0.05).

In table III, the relationship between hypophosphatemia and the other variables (age,FEV_1, FVC, FEV_1/FVC, FEF_{25-75}, PEF,pH, pCO_2, pO_2,O_2 saturation) are shown. Only pH values were found significantly lower in the patients having hypophosphatemia than the group with normal P level (p<0.05).

Discussion

Hypophosphatemia is a frequent laboratory finding seen in hospitalized patients. Prevalence of hypophosphatemia ranges from 2 to 5 % in patients who are hospitalized for any reason. The prevalence increases to 20-40% in patients with alcoholism, diabetic ketoacidosis or sepsis. Although there have not been enough studies investigating the prevalence of hypophosphatemia in COPD patients, a prevalence of 25% for hypophosphatemia has been described in patients with respiratory illness (5). Fiaccadori et al.(3) had reported in their study a prevalence of 20 % in COPD patients. In our study we also found a hypophosphatemia prevalence 20 percent in the COPD patients. Fiaccadori et al (3) found in their study a significant correlation between serum and muscle P content of 14 patients with COPD. They had reported that in all cases with hypophosphatemia, muscle phosphorus content was also found low. Two out of 14 patients had normal serum P level but reduced muscle P content. In our study, we also found muscle P content lower in cases with hypophosphatemia than the group with normal serum level. But this correlation was not statistically significant

Table I: Hypophosphatemia prevalence and the distribution with the stage of the disease.

	n (%)	Stage n (%)	Stage 3 n (%)
Hypophosphtamia (P<2.5mg/dl)	3 (20)	1 (16.7)	2 (22.2)
Normal Serum Phosphorus (P≥2.5mg/dl)	12 (80)	5 (83.3)	7 (77.8)

Table II: Distribution of mean serum and muscle phosphorus values according to hypophosphatemia and normal serum phosphorus level.

	n	Serum Phosphorus X±SD mg/dl	Muscle Phosphorus X±SD mg/dl FFS
Hypophosphatemia (P<2.5mg/dl)	3	2.06±0.23	3034.00±1413.98
Normal Serum Phosphorus (P≥2.5 mg/dl)	12	3.37±0.43	3549.08±1599.50

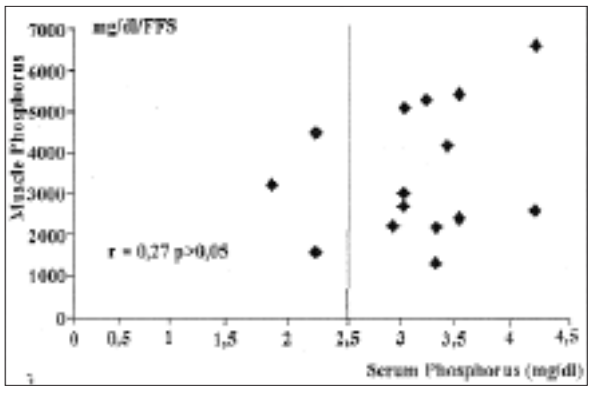

Figure 1: Relationship between serum and muscle phosphorus in COPD patients.

(p>0.05). We could not determine the normal ranges of muscle P content because there was not a control group in our study. One of the causes of hypophosphatemia is the transcellular shift of phosphorus. The serum level and muscle P content were not studied at the same time and this also might affect the results. Muscle biopsies were not performed in the first days of the hospitalization while the clinics of patients were not good enough. So during this time, patients had received theophylline treatment in dextrose solution with other drugs and thereby alterations were seen in arterial blood gases and pH values.

Glucose infusion induces a release of insulin which promotes the shift of both glucose and P into the cells (6,7). In our study we found statistically significant correlation between low pH values and hypophosphatemia (p<0.05). The alterations in pH also affect the serum and muscle P content. Respiratory acidosis inhibits the anaerobic glycolysis and increases both serum P level and urinary P excretion. So total body phosphorus content reduces seriously in respiratory acidosis. When the pH returns to normal, hypophosphatemia may develop because of increased shifts of phosphorus from blood into the cells secondary to increased glycolytic activity (6,8,9). Statistically nonsignificant correlation between hypophosphatemia and muscle P content might be due to the transcellular P shift caused by the glucose infusion and alterations of arterial blood gases and pH values.

There have not been enough studies showing the relationship between the severity of COPD and hypophosphatemia and low phosphorus content of muscle. We performed the staging according to the ATS criteria to determine this relationship. Forty percentage of cases were in stage II, 60 % were in stage III. Although patients who were in stage III had lower serum and muscle phosphorus content than the group with stage II, nonsignificant correlation was found between the stage of the disease and serum and muscle phosphorus level (p>0.005). Number of patients included into the study were few and there was no control group, so the results might be statistically nonsignificant because of this reason. Lotz et al.(10) have described muscular weakness in human beings having experimental phosphate depletion. More recently, it has also been shown that the diaphragm is more sensitive to fatigue in phosphate depleted dogs (11).

Aubier et al. (12) had studied the effects of hypophosphatemia on diaphragmatic function in

Table III: The relationship between hypophosphatemia and normal serum phosphorus level and the other variables.

	Hypoposphatemia (P<2.5 mg/dl) X±SD n: 3	**Normal Serum Phosphorus X±SD n: 12**
Age	54.00±5.19	64.00±13.41
FEV_1 (%)*	27.66±12.42	34.00±15.17
FEVC (%)*	49.33±27.31	44.80±21.89
FEV_1/FVC (%)*	54.00±28.16	62.80±16.85
FEF_{25-75} (%)*	12.66± 4.93	23.20±16.21
PEF (%)*	28.33±10.59	30.60±14.60
pH	7.28± 0.01**	7.33± 0.05
PCO_2 (mmHg)	43.00±12.49	45.08±14.04
PO_2 (mmHg)	55.33±16.04	54.91±17.96
O_2 Saturation (%)	81.00±12.12	82.58± 7.54
HCO_3 (mmol/l)	20.46± 5.46	24.41± 7.10
Creatine clearence (ml/sec)	67.33±15.37	78.00±17.33

* Percentage of predicted value ** p<0.05

8 patients with acute respiratory failure who were artificially ventilated. They had reported that hypophosphatemia might impair the contractile properties of the diaphragm during acute respiratory failure. They found elevation of transdiaphragmatic pressure in all patients after correction of hypophosphatemia. The increase in transdiaphragmatic pressure could have been due to the changes in the length and curvature of the diaphragm. A major determinant of the length and curvature of the diaphragm is the lung volume. They suggested that the increase in transdiaphragmatic pressure in patients after correction of hypophosphatemia could have reflected a decrease in their functional residual capacity.

Hypophosphatemia increases the hemoglobin-oxygen affinity as a result of 2-3 diphosphoglycerate concentration reduction in red cells. This may be effective in the progress of respiratory failure (5).

In our study we also found that in patients with hypophosphatemia the course of COPD was more severe. Although the results were not statistically significant, these findings suggest that hypophosphatemia may also make a contribution for the development of respiratory failure in COPD. But further detailed studies, having more patients and control groups, are needed to evaluate the relationship between severity of COPD and the serum and muscle phosphorus content.

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