Phosphate diabetes in patients with chronic fatigue syndrome

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Summary

Phosphate depletion is associated with neuromuscular dysfunction due to changes in mitochondrial respiration that result in a defect of intracellular oxidative metabolism. Phosphate diabetes causes phosphate depletion due to abnormal renal re-absorption of phosphate by the proximal renal tubule. Most of the symptoms presented by patients with phosphate diabetes such as myalgia, fatigue and mild depression, are also common in patients with chronic fatigue syndrome, but this differential diagnosis has not been considered. We investigated the possible association between chronic fatigue syndrome and phosphate diabetes in 87 patients who fulfilled the criteria for chronic fatigue syndrome. Control subjects were 37 volunteers, who explicitly denied fatigue and chronic illness on a screening questionnaire. Re-absorption of phosphate by the proximal renal tubule, phosphate clearance and renal threshold phosphate concentration were the main outcome measures in both groups. Of the 87 patients with chronic fatigue syndrome, nine also fulfilled the diagnostic criteria for phosphate diabetes.

In conclusion, we report a previously undefined relationship between chronic fatigue syndrome and phosphate diabetes. Phosphate diabetes should be considered in differential diagnosis with chronic fatigue syndrome; further studies are needed to investigate the incidence of phosphate diabetes in patients with chronic fatigue syndrome and the possible beneficial effect of vitamin D and oral phosphate supplements.

Keywords: phosphate diabetes; chronic fatigue syndrome; renal tubular reabsorption

Chronic fatigue syndrome (CFS) is a disabling illness of unknown cause, mainly characterised by unexplained, disabling fatigue lasting more than six months, myalgia, and neuropsychological symptoms.¹ The differential diagnosis has been proposed to include a number of medical conditions such as cardiovascular disorders, infectious diseases, sleep disorders, autoimmune disorders, depression, endocrine disorders, haematological problems, respiratory disorders, metabolic disorders, sarcoidosis, and fibromyalgia.² Most of the symptoms

presented by CFS patients are also common in patients with phosphate diabetes (PD),³ but this differential diagnosis has not previously been considered. PD is diagnosed when the phosphate clearance is greater than 15 ml/min and/or the phosphate tubular re-absorption (PTR) is below 85%.^{4,5} Laroche *et al*⁶ have also observed that PD patients have a renal threshold phosphate concentration ($TmPO_4/GFR$) below 0.8 mmol/l.

The aim of this study was to investigate the possible association between CFS and PD by the analysis of the phosphate clearance, PTR, and $TmPO_4/GFR$ in a large group of patients diagnosed as having CFS.

Patients and methods

Between December 1995 and June 1996, 87 patients who fulfilled the Centre for Disease Control (CDC) criteria of the working case definition of CFS¹ were observed at our centre and submitted to clinical and laboratory evaluation. All subjects had history of debilitating fatigue lasting more than six months and fulfilled six or more CDC minor criteria. Before being seen in consultation, CFS patients had first indicated on a self-administered screening questionnaire that they had experienced debilitating chronic fatigue for at least the past six months. Patients whose questionnaire, interview, examination, or medical record revealed medical conditions associated with chronic fatigue such as chronic infections, parasitic infections, neuromuscular diseases or connective tissue disorders were excluded, as were patients with autoimmune diseases, cardiovascular diseases, malignancies, severe gastrointestinal disorders, endocrine diseases, haematological and renal diseases and psychiatric disorders.

SELECTION OF CONTROL SUBJECTS

Control subjects were 37 volunteers, who explicitly denied fatigue and chronic illnesses on a screening questionnaire. All control subjects underwent physical examination and laboratory investigations to assess their general health. None of the control subjects had experienced a period of fatigue or unexplained malaise lasting more than one week, in the six months preceding assessment.

LABORATORY TESTING

Urine sodium and potassium were measured by flame photometry. Serum and urine calcium and phosphate were assayed on the Technicon

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DAX 48 analyser using manufacturer’s recommended methods; calcium by cresolphthalein complex formation and phosphate by complexation with ammonium molybdate. Serum and urine creatinine were measured using the Jaffe reaction on the DAX 48 (Bayer Diagnostics, Basingstoke, Hants, UK).

Calculated parameters included phosphate clearance, PTR and renal phosphate threshold. Phosphate clearance was calculated using the formula:

$$\frac{\text{urine phosphate (mmol/l)} \times \text{urine volume (ml)}}{\text{serum phosphate (mmol/l)} \times \text{time (min)}}$$

Calculation of PTR used the formula:

$$\frac{(\text{urine phosphate (mmol/l)} \times \text{serum creatinine (mmol/l)})}{(\text{urine creatinine (mmol/l)} \times \text{serum phosphate (mmol/l)})}$$

The renal threshold phosphate concentration was obtained using the nomogram derived by Walton and Bijvoet which uses the actual plasma phosphate concentration and the PTR.⁷ Parathyroid hormone was determined using a radioimmunoassay (Nichols Institute Diagnostics, Newport, Essex UK) using iodinated parathyroid hormone as tracer. Vitamin D was measured using a radioimmunoassay (Incstar Limited, Wokingham, Berks, UK) using oxidated 25-hydroxycholecalciferol as tracer. In all subjects, the blood tests were performed after 12 hours fasting, at 09.00 h.

STATISTICAL ANALYSIS

All analysis was carried out using the SPSS package. Data was checked for outliers and normality of distribution. Normally distributed variables were compared using the unpaired *t*-test whilst non-normally distributed variables were compared using the Mann-Whitney U-test statistic.

Results

This study analysed data from 87 CFS patients and 37 healthy controls. The mean age, sex, body mass index, serum phosphate, calcium, creatinine, and alkaline phosphatase, and the 24-hour urine excretion of calcium, phosphate, chloride, sodium, magnesium, creatinine and potassium for both groups are given in the table.

There was no significant difference in the mean values between the two groups for any of the parameters with the exception of mean serum phosphate concentration, which was found to be significantly lower in CFS patients (1.09 *vs* 1.17 mmol/l, *p*=0.01) than in control subjects, although the mean remained within the reference range. Serum vitamin D and parathyroid hormone concentrations were measured in a subset of patients and controls; the mean values were not significantly different between the two groups (table).

There was no significant difference in the mean values for phosphate clearance, PTR and TmPO₄/GFR between the CFS patient group and the controls. However, 12 patients with CFS were found to have a phosphate clearance greater than 15 ml/min and/or a PTR below 85% (data not shown). Moreover, nine of these patients showed a phosphate clearance greater than 15 ml/min, a PTR below 85%, and a TmPO₄/GFR below 0.80 mmol/l. Therefore, in our group of 87 CFS patients, approximately 14% also fulfilled the diagnostic criteria for PD, although the clinical symptoms in these nine patients did not show significant differences when compared to symptoms of CFS patients without PD. In all 37 control subjects the TmPO₄/GFR was greater than 0.80 mmol/l, and none fulfilled the abovementioned diagnostic criteria for PD. The distribution of serum phosphate, phosphate clearance, and PTR and TmPO₄/GFR are shown in the figure.

Table Clinical details, calcium and phosphate serum concentrations, 24 h urine excretion, renal tubular tests, parathyroid hormone and vitamin D serum levels in 87 CFS patients and 37 controls

	Healthy (n=37)		CFS (n=87)		P
	Mean	SD	Mean	SD	
Age (years)	42.9	8.9	41.6	11.0	0.55
Male : female ratio	43 : 57		51 : 46		
BMI (kg/m ²)	23.1	3.1	23.7	4.0	0.48
Serum phosphate (mmol/l)	1.17	0.15	1.09	0.16	0.01
Calcium (mmol/l)	2.3	0.1	2.3	0.1	0.29
Creatinine (μmol/l)	74.4	11.3	77.9	12.5	0.15
24 h urine					
Calcium (mmol/24 h)	4.0	1.6	4.6	2.3	0.26
Chloride (mmol/24 h)	156.6	64.7	79.9	38.2	0.26
Creatinine (mmol/24 h)	12.5	3.5	12.9	4.0	0.61
Magnesium (mmol/24 h)	4.1	2.1	4.4	1.9	0.61
Phosphate (mmol/24 h)	15.0	10.2	13.4	6.5	0.30
Potassium (mmol/24 h)	88.6	26.4	80.4	22.8	0.09
Sodium (mmol/24 h)	144.9	66.4	146.7	60.4	0.89
Phosphate clearance (ml/min)	15.3	6.8	15.4	6.4	0.92
PTR (%)	86.9	4.0	86.7	4.0	0.79
TmPO ₄ /GFR (mmol/l)	1.09	0.16	1.07	0.23	0.57
Alkaline phosphatase (IU/l)	54.1	17.7	54.1	12.9	0.99
Vitamin D (μg/l)*	16.0 (n=11)	7.1	18.2 (n=23)	7.9	0.46
Parathyroid hormone (ng/l)*	29.2 (n=10)	16.9	36.0 (n=25)	17.7	0.24

TmPO₄/GFR=Renal Threshold Phosphate Concentration; BMI=Body Mass Index; PTR=phosphate tubular reabsorption. All quoted *p*-values are from unpaired *t*-test except*=Mann-Whitney U-test statistic.

Figure Distribution of serum phosphate, phosphate tubular re-absorption, phosphate clearance and renal threshold phosphate concentration ($TmPO_4/GFR$) in 87 CFS patients and 37 controls

Discussion

Previous studies of patients with CFS have demonstrated a markedly reduced dynamic exercise capacity, in the absence of clinical neuromuscular dysfunction, suggesting the possibility of a subclinical defect of skeletal muscle.⁸ Wong *et al*⁹ showed that CFS patients reach exhaustion much more rapidly than normal subjects and that they also have relatively reduced intracellular concentrations of adenosine triphosphate (ATP). They concluded that a defect of oxidative metabolism may contribute to the reduced physical endurance of CFS patients.

On the other hand, Barnes *et al*¹² did not find consistent abnormalities of glycolysis, mitochondrial metabolism or pH regulation in a group of 46 CFS patients studied with a phosphorus magnetic resonance spectroscopy. However, they showed increased acidification relative to phosphocreatine depletion and reduced acidification in a subgroup of these patients.

Several studies showed changes in mitochondrial respiration, with decreased production of intracellular ATP in patients with chronic hypophosphataemia and intracellular phosphate depletion.^{10, 11} The neuromuscular alterations resolved when serum phosphate levels returned to normal.¹⁰

One study evaluated the effect of moderate and prolonged phosphate depletion on cellular energy production, transfer and utilisation of skeletal muscle in rats fed a phosphate-deficient diet.¹³ The results of this study demonstrated that dietary phosphate restriction in the rat is associated with marked alterations in the various steps of energy metabolism. The main finding of reduced mitochondrial oxygen consumption and phosphorylation points towards an impairment in mitochondrial energy production. Possibly phosphate depletion caused a reduction in protein synthesis and consequently a reduction in the activity of many enzymes.

It is still difficult to explain in detail how phosphate depletion, even when severe, can give rise to abnormalities of muscle bioenergetics. There is little agreement on the mechanism of any of the cellular effects of abnormalities of phosphate metabolism.¹⁴ Furthermore, even quite large changes in plasma phosphate may give rise to only small changes in muscle cell phosphate concentration.¹⁵ On the other hand, mild dietary phosphate depletion can reduce muscle cell phosphate concentration without change in plasma phosphate, although without detectable effect on muscle bioenergetics.¹⁶

Substantial variations in serum phosphate levels have been found from one day to the next, and even during a given day, with near-normal values on some occasions.⁶ Serum phosphate concentration is in all probability a poor indicator of phosphate deficiency. This, together with the fact that mean laboratories set the lower limit of normal at 0.8 mmol/l, explains the mean interval of six years between symptom onset and diagnosis of PD.⁶ The distinctive symptoms of PD, myalgia, fatigue, and depression, are probably not directly due to the hypophosphataemia since patients with PD do not respond immediately to correction of serum phosphate.¹⁷

Compounding all these data from the literature,^{9, 12-16} it appears that the mechanism that leads to neuromuscular alterations in the presence of mild phosphate depletion is not yet fully understood.

One reason why CFS patients should have a decrease in oxidative metabolism is probably related to a metabolic defect that is secondary to a state of chronic underutilisation of skeletal muscle.¹⁸⁻²¹ If the 'deconditioning' of skeletal muscle is a clinical reality, CFS patients may be subject, in some degree, to its metabolic effect.²² The second causal hypothesis is that an unknown trigger factor directly depresses muscle metabolism. The alterations in muscle membrane potential and in calcium transport through the sarcolemma that have been demonstrated in chronic hypophosphataemia suggests that intracellular phosphate depletion may be involved in the genesis of the

symptoms.⁵ These alterations also induce changes in mitochondrial respiration, with decreased production of intracellular ATP,^{5 10} as has been previously found in CFS patients.⁹

It is clear that renal re-absorption of phosphate by the proximal tubule is the main mechanism underlying phosphate homeostasis.¹⁰ Phosphate diabetes due to an abnormal renal re-absorption of phosphate can cause phosphate depletion. In our study, nine patients with CFS matched the diagnostic criteria for PD. Until now PD has not been associated with CFS, it has not been considered in differential diagnosis with CFS and the incidence of PD in patients with CFS is not known. The importance of investigating the incidence of PD in patients with CFS is related to the potential beneficial effects that could result from the treatment of PD. In fact, oral phosphate supplements and vitamin D have been shown to restore plasma phosphate concentration and muscle biochemistry to normal and to produce considerable improvement in symptoms and exercise tolerance in PD patients.¹⁸ Land *et al*²³ also described a patient with idiopathic renal hypophosphataemia and

previously undiagnosed fatigue in whom normalisation of plasma phosphate by oral phosphate supplementation caused a marked improvement in symptoms and biochemical muscle abnormalities despite little changes in muscle phosphate concentration.

The rationale of administration of phosphate supplement and vitamin D is that this combination restores phosphate homeostasis in PD patients, while in patients with hypophosphataemia, vitamin D increases active intestinal absorption of phosphate.²⁴

We conclude that it is of clinical significance to exclude the presence of PD, using the diagnostic criteria mentioned above, in patients with CFS. The TmPO₄/GFR should be routinely determined in patients whose serum phosphate level is under 0.9 mmol/l.^{6 7 23 25} Further studies are needed to investigate the incidence of PD in patients with CFS and the effects of oral phosphate supplements and vitamin D.

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