



# The relationship between phosphorus level and peak oxygen uptake in hemodialysis patients awaited for renal transplantation

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## ABSTRACT

**Introduction:** End-stage renal disease (ESRD) is one of the most common diseases, which affects many aspects of patients' lives. The measurement of exercise capacity through peak oxygen uptake is an important factor in predicting mortality and survival in patients with ESRD.

**Objectives:** In the current study, we aimed to examine the relationship between phosphorus level and  $VO_2$  uptake in renal transplant candidates receiving hemodialysis.

**Patients and Methods:** Thirty renal transplant candidates on hemodialysis were evaluated through spirometry and exercise tests. Then, the results were compared according to the inclusion criteria of age, gender, and phosphorus level.

**Results:** All of cases were male with the mean age of  $37.93 \pm 10.48$  years (range; 20-55 years). Mean  $VO_2$  max was  $23.46 \pm 8.22$  mL/kg/min (range; 6.88 to 43.44 mL/kg/min). The mean phosphorus level was  $6 \pm 2.3$  mg/dL (range; 2-10.6 mg/dL) since eight patients had high levels of phosphorus (more than 5.5 mg/dL). In patients with low phosphorus level an abnormal  $VO_2$  max was detected ( $P = 0.027$ ). Furthermore, Fisher's exact test reflected a significant association between higher levels of phosphorus with normal  $VO_2$  max ( $P = 0.029$ ).

**Conclusion:** In hemodialysis, decreased blood phosphorus is a predisposing factor for reduced exercise capacity, while hypophosphatemia may lower  $VO_2$  max through reducing energy of skeletal muscles. The relationship between phosphorus level and  $VO_2$  max may be related to morbidity in hemodialysis patients. Hence, treatment modalities reducing serum levels of phosphorus should be conducted with caution in some patients.

### Implication for health policy/practice/research/medical education:

In a study on 30 ESRD patients awaiting renal transplantation, we found, decreased blood phosphorus is a predisposing factor for decreased exercise capacity, while hypophosphatemia may lower maximal oxygen uptake ( $VO_2$  max) through reducing energy of skeletal muscles. In fact, ideal control of phosphate level in CKD is important to avoid complications of secondary hyperparathyroidism. Nevertheless, too low phosphate level may present a risk for disturbed pulmonary function and exercise capacity.

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## Introduction

End-stage renal disease (ESRD) is the final stage of chronic kidney disease (CKD), in which the kidneys no longer function well enough to meet the needs of daily life (1,2). The treatments for ESRD are dialysis or kidney transplant (3,4). The worldwide rise in the number of patients with CKD and its consequent named end-stage renal failure need renal replacement therapy (5). Although the improvement in survival of patients undergoing

maintenance dialysis in the United States is detectable, however, mortality continues to be unacceptably high, approaching 20% per year (6-9).

Functional capacity of ESRD patients is dramatically impaired, since CKD patients treated with dialysis are characterized by a severely limited exercise capacity (10,11).

Maximal oxygen uptake ( $VO_2$  max) is a predictor of postoperative mortality. Maximal oxygen uptake level

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in CKD is 59.3% of the age-predicted  $\text{VO}_2$  max level in normal controls (12). In fact, low  $\text{VO}_2$  and self-reported functioning were shown to be predictive of poor outcomes in dialysis patients (13). Contributing factors include hypertension, glucose intolerance, dyslipidemia, high serum homocysteine concentrations, and abnormalities in calcium and phosphorus metabolism (14). Many of these disturbances are present in children and young adults with ESRD. Phosphorus, as an important mineral for cell structure and energy, circulates less than 1% in the serum, the “exchangeable phosphorus pool” as suggested by Hruska et al (15). In normal subjects, the skeleton remains neutral (equal exit and entry) regarding phosphorus homeostasis and the kidneys regulate phosphorus balance (16,17). In renal disease, the kidney fails to excrete phosphorus and the result is a positive phosphorus balance (18). Elevated serum phosphate is a common complication among ESRD patients, affecting up to 70% of dialysis patients (19,20). Increased serum phosphorus level is associated with high mortality rate. In spite of dietary restrictions, individuals receiving dialysis invariably experience hyperphosphatemia (21). Dietary restriction of phosphorus and dialysis prescription are unable to maintain phosphorus level within the recommended range (below 5.5 mg/dL) in patients with advanced ESRD.

### Objectives

Given the paucity of studies on this issue and the importance of both phosphorus and  $\text{VO}_2$  max in ESRD, we aimed to assess the relationship between phosphorus level and  $\text{VO}_2$  uptake in renal transplant candidates receiving hemodialysis therapy.

### Patients and Methods

#### Study population

We studied 30 patients with chronic renal failure. We performed pulmonary function testing (PFT) and cardiopulmonary exercise test (CPET) for all the subjects. The main inclusion criterion was the stability of patients for performing the exercise test. The exclusion criteria comprised of active infectious and inflammatory diseases, malignancy, malnutrition, atopy and asthma, history of myocardial infarction, walking disability, arthritis and arthralgia, disability and exertion-limiting cardiac diseases.

#### Laboratory assessments

Venous blood samples were collected to measure the level of serum phosphorus. We considered other factors that might limit exercise capacity. Symptom-limited or maximal-heart-rate testing (CPET) was conducted by a cycle ergometer (ergo-metrics 900, SensorMedics, Bilthoven, The Netherlands) and a spirometer. Patients were advised not to eat or drink several hours before exercise testing. The gas analyzer was calibrated just

before the investigation. A facemask connected to a low-resistance unidirectional valve was placed on the patients' face and checked for leakage. The incremental exercise test consisted of a 3-minute baseline resting period, followed by a 3-minute warm-up period (up to 60 rpm pedaling), and subsequent periodic work increased by 15 watts each minute. For each patient, during ECG testing, blood pressure and oxygen saturation were regularly monitored. When the heart rate reaches a maximum level or the exercise-limiting signs are observed, then the ECG was stopped.

#### Ethical issues

The research followed the tenets of the Declaration of Helsinki. Informed consent was obtained. The ethical committee of Mashhad University of Medical Sciences approved the research (Ref #98/94073). All patients' information remained confidential. This study was extracted from M.D thesis of Saba Khajeh Dargi (Thesis #6812) and supported by the Kidney Transplantation Complications Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

#### Statistical analysis

The normality of data was tested by using Kolmogorov-Smirnov test. Parametric variables were extracted as mean  $\pm$  standard deviation (SD). Categorical data were stated as percent and compared by Fisher's exact test. T-test was used to compare differences between groups. The data were analyzed by SPSS version 16. The Pearson's correlation test was used to evaluate the relationship between serum phosphorus and  $\text{VO}_2$  max. In this study, *P* values below 0.05 were considered as statistically significant for all tests.

### Results

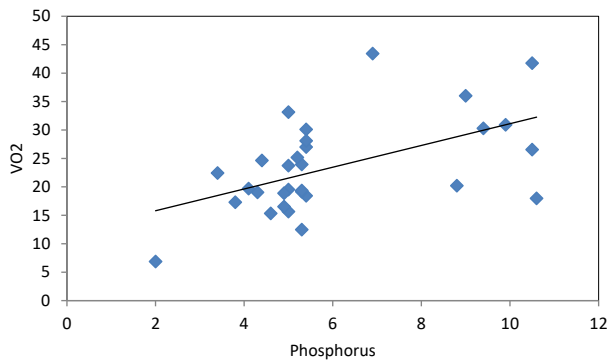
All patients were male with the mean age of  $37.93 \pm 10.48$  years (age range; 20-55 years). The  $\text{VO}_2$  max was  $23.46 \pm 8.22$  ml/kg/min (range; 43.44-6.88 mL/kg/min). Maximum and minimum levels of phosphorus were 10.6 mg/dL and 2 mg/dL, respectively, with the mean level of ( $6 \pm 2.3$  mg/dL).

Based on  $\text{VO}_2$  max, we divided all the cases into two groups of normal ( $\geq 20$  ml/kg/min) and abnormal ( $< 20$  mL/kg/min).

Pearson's correlation analysis revealed a direct relationship between serum phosphorus level and  $\text{VO}_2$  uptake ( $r = 0.71$ ,  $P = 0.02$ ; Figure 1). According to Fisher's exact test, patients with low phosphorus levels presented abnormal  $\text{VO}_2$  max ( $P = 0.027$ ; Tables 1 and 2).

### Discussion

Reduced peak oxygen uptake (peak  $\text{VO}_2$ ) is a prognosticator of mortality in various chronic diseases during the preoperative period. Low peak  $\text{VO}_2$  in CKD patients can be due to different circumstances comprising, electrolyte imbalance, cardiovascular diseases, anemia,



**Figure 1.** Association between phosphorus level and oxygen uptake ( $VO_2$ ).

**Table 1.** Mean and standard deviation of demographic data, phosphorus, and oxygen uptake ( $VO_2$ )

Variable	Mean± SD	Range
Age (y)	37.93±10.48	(20-55)
Weight (kg)	65.23±14.78	(43-101)
Phosphorus (mg/dL)	6 ±2.31	(2-10.6)
$VO_2$ max (mL/kg/min)	23.46±8.22	(6.88-43.44)

**Table 2.** Phosphorus level and maximal oxygen uptake ( $VO_2$  max)

Phosphorus level	Maximal oxygen uptake (mL/kg/min)		P value
	<20 No. (%)	≥20 No. (%)	
Hypo	1 (50)	1 (50)	0.027
Normal	12 (60)	8 (40)	
Hyper	1 (12.5)	7 (87.5)	

malnutrition, active infections and hyperparathyroidism (22-25).

In this study, we found a significant relationship between low-serum phosphate level and decreased  $VO_2$ . Various investigations have revealed that peak  $VO_2$  is a predictor of postoperative mortality (26, 27) in individuals with kidney insufficiency waiting for renal transplantation (13). Phosphorus is the main component of adenosine 5'-triphosphate (ATP) in energy-related mechanisms operating in muscles of the respiratory and musculoskeletal systems (28).

On the other hand, hyperphosphatemia is a serious problem due to secondary hyperparathyroidism in chronic renal failure patients. Phosphorus-binding agents are recommended to control serum phosphate level in these individuals (29, 30). Ulubay et al studied the factors affecting exercise capacity in renal transplantation candidates receiving continuous ambulatory peritoneal dialysis therapy (31). Correspondingly, they found that peak  $VO_2$  was well correlated with serum phosphate

level. They found, 96% the patients terminated cardiopulmonary exercise testing due to tiredness in leg. They explained this mechanism of exercise limitation as peripheral and respiratory muscle weakness due to low-serum phosphorus level in individuals with ESRD.

Ideal control of phosphate level in CKD individuals is important to avoid complications of secondary hyperparathyroidism. Nevertheless, too low phosphate level may present a risk for disturbed pulmonary function and exercise capacity. Based on our findings, we conclude that treatment modalities that lower serum phosphorus level should be applied with caution in individuals with kidney insufficiency. High perioperative risk is an absolute contraindication for kidney transplantation. Peak oxygen uptake is a valuable interpreter of perioperative mortality. The results of this investigation suggest that parameters decreasing oxygen uptake (like phosphorus-binding agents that might lower serum phosphorus level) must be monitored closely and considered during the preoperative period in individuals with end-stage kidney insufficiency waiting for transplantation.

In our study, all the studied patients were candidate for renal transplantation. In a study to find, the consequence of kidney transplantation on pulmonary function and respiratory muscle strength in patients with end-stage kidney failure, Guleria et al showed that transplantation resulted in a significant improvement in pulmonary and respiratory muscle function (32). This may confirm our findings regarding the fact that decreased  $VO_2$  max diminished the energy of skeletal muscles. Development of new phosphate binders and efforts to find new ways to inhibit gastrointestinal absorption of phosphate might improve management of serum phosphate level in ESRD patients.

## Conclusion

In renal transplant patients, elevated phosphorus level can be the sole predisposing factor for decreased exercise capacity. Hypophosphatemia may decrease the  $VO_2$  max by reducing energy of skeletal muscles. Regarding, the relationship between phosphorus and  $VO_2$  max, patients' survival can be enhanced in patients with ESRD awaiting renal transplantation. However, treatment modalities diminishing serum phosphorus level should be applied with caution in these patients.

## Limitations of the study

This study was conducted on a limited proportion of patients. We suggest larger studies on this feature of hemodialysis patients.

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### Authors' contribution

HB, MM, KS and AA conducted the research. KS conducted the statistical analysis. HB prepared the primary draft. AA revised and prepared the final manuscript. All authors read and approved the final paper.

### Conflicts of interest

There were no points of conflict to declare.

### Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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