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

Boshra Hasanzamani, Mohamad Javad Mojahedi, Saba Khajeh Dargi, Amir Mohamad Hashem Asnaashari

1Kidney Transplantation Complications Research Center, Department of Internal Medicine, Ghaem Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
2Mashhad University of Medical Sciences, Mashhad, Iran

*Corresponding author: Amir Mohamad Hashem Asnaashari, Email: AsnaashariAM@mums.ac.ir

**Keywords:**
End-stage renal disease
Phosphorus
Maximal oxygen uptake
Renal transplantation
Chronic kidney disease

**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 VO2 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±10.48 years (range; 20-55 years). Mean VO2 max was 23.46±8.22 mL/kg/min (range; 6.88 to 43.44 mL/kg/min). The mean phosphorus level was 6±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 VO2 max was detected (P=0.027). Furthermore, Fisher's exact test reflected a significant association between higher levels of phosphorus with normal VO2 max (P=0.029).

**Conclusion:** In hemodialysis, decreased blood phosphorus is a predisposing factor for reduced exercise capacity, while hypophosphatemia may lower VO2 max through reducing energy of skeletal muscles. The relationship between phosphorus level and VO2 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 (VO2 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.

in CKD is 59.3% of the age-predicted VO\textsubscript{2}\text{max} level in normal controls (12). In fact, low VO\textsubscript{2} max 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 VO\textsubscript{2} max in ESRD, we aimed to assess the relationship between phosphorus level and VO\textsubscript{2} max 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 ± 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 VO\textsubscript{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 37.9±10.48 years (age range; 20-55 years). The VO\textsubscript{2} max was 23.46±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 (6.2.3 mg/dL).

Based on VO\textsubscript{2} max, we divided all the cases into two groups of normal (≥20 ml/kg/min) and abnormal (<20 ml/kg/min).

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

Discussion
Reduced peak oxygen uptake (peak VO\textsubscript{2}) is a prognosticator of mortality in various chronic diseases during the preoperative period. Low peak VO\textsubscript{2} in CKD patients can be due to different circumstances comprising, electrolyte imbalance, cardiovascular diseases, anemia,
Phosphorus level and peak oxygen uptake

Figure 1. Association between phosphorus level and oxygen uptake (VO\textsubscript{2}).

Table 1. Mean and standard deviation of demographic data, phosphorus, and oxygen uptake (VO\textsubscript{2} max)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>37.93±10.48</td>
<td>(20-55)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.23±14.78</td>
<td>(43-101)</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>6±2.31</td>
<td>(2-10.6)</td>
</tr>
<tr>
<td>VO\textsubscript{2} max (mL/kg/min)</td>
<td>23.46±8.22</td>
<td>(6.88-43.44)</td>
</tr>
</tbody>
</table>

Table 2. Phosphorus level and maximal oxygen uptake (VO\textsubscript{2} max)

<table>
<thead>
<tr>
<th>Phosphorus level</th>
<th>Maximal oxygen uptake (mL/kg/min)</th>
<th>&lt;20 No. (%)</th>
<th>≥20 No. (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypo</td>
<td></td>
<td>1 (50)</td>
<td>1 (50)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td>12 (60)</td>
<td>8 (40)</td>
<td>0.027</td>
</tr>
<tr>
<td>Hyper</td>
<td></td>
<td>1 (12.5)</td>
<td>7 (87.5)</td>
<td></td>
</tr>
</tbody>
</table>

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

In this study, we found a significant relationship between low-serum phosphate level and decreased VO\textsubscript{2}. Various investigations have revealed that peak VO\textsubscript{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, hypophosphatemia 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\textsubscript{2} was well correlated with serum phosphate level. They found, 96% of 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\textsubscript{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\textsubscript{2} max by reducing energy of skeletal muscles. Regarding, the relationship between phosphorus and VO\textsubscript{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.

Acknowledgments
We would like to thank all staff of spirometry and Sports Sciences Department of Ghaem Hospital, Mashhad University of Medical Sciences, and all those who have helped us in this study.
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.

Funding/Support
This study was extracted from MD thesis of Saba Khajeh Dargi (#6812) and supported by the Kidney Transplantation Complications Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.

References


Copyright © 2020 The Author(s); Published by Nickan Research Institute. This is an open-access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.