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TANAFFOS

The Effect of Renal Transplantation on Respiratory Muscle Strength in Patients with End Stage Renal Disease

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Background: There is evidence of musculoskeletal and respiratory involvement in patients with chronic kidney disease (CKD). This is attributed to protein calorie imbalance that is caused by the disease process, and hemodialysis and is generally referred to as uremic myopathy. This results in calcification of respiratory muscles such as diaphragm and intercostal muscles. There are limited data about respiratory muscle strength in patients with CKD. We intended to evaluate the effect of kidney transplantation on respiratory muscles strength in patients with CKD.

Materials and Methods: Spirometry was used to measure maximal inspiratory mouth pressure (P_{IMAX}), which was calculated by using the lung residual volume and maximal respiratory pressures at the mouth (P_{EMAX}), 2 days before and again 30 days after kidney transplantation in 26 patients with ESRD. PIMAX and PEMAX values less than 60% of the predicted value were considered abnormal.

Results: Mean ± SD PIMAX values showed significant increase from 31.88 ± 8.58 cmH2O before kidney transplantation to 37.65 ± 13.39 cmH2O after transplant ($P < 0.001$). Similarly, a significant increase in PEMAX values was observed from 33.04 ± 16.12 cmH2O to 39.19 ± 20.34 cmH2O ($P < 0.001$). Nineteen patients (73.1%) showed significant increases in PIMAX and PEMAX values. Mean serum creatinine decreased from 6.94 to 1.32 ($P < 0.001$) after transplant.

Conclusion: Although both PIMAX and PEMAX values increased significantly after kidney transplant, these measurements were still below lower limit of normal. This suggests that factors other than uremic myopathy may contribute to respiratory muscle weakness in patients CKD.

Key words: Chronic kidney disease, Kidney transplant, Maximal inspiratory pressure (PIMAX), Maximal expiratory pressures (PEMAX)

INTRODUCTION

Chronic kidney disease not only deteriorates renal function, but also affects other organs, including respiratory system muscles. This, in addition to the effects of hemodialysis, may weaken the respiratory muscles of patients with CKD (1-3). In fact, patients with CKD who receive hemodialysis are less active and suffer from muscle weakness and atrophy (4). This is related to several factors such as anemia, malnutrition, protein-calorie imbalance, decreased serum calcium level, decreased oxidative stress, etc. Uremia exerts its detrimental effects on muscles via intravascular calcification and decreased blood flow. Respiratory muscles are no exception to these effects (5-7). Decreased respiratory muscle strength in CKD patients has been reported in previous studies (8). It has been shown that longer duration of hemodialysis dependence is associated with decreased strength of respiratory muscles (9). These changes have been noted clinically and histologically and microscopic evaluation of muscle fibers of patients with CKD has shown structural abnormality and myopathy (3).

Patients with CKD may suffer some adverse effects related to their myopathy. In addition to decreased quality of life, patients with respiratory muscle myopathy suffer from decreased ventilation, which may result in pleural effusion, dyspnea, and hypoxia (9). A few small studies have indicated that kidney transplant may significantly improve muscle strength and pulmonary function of patients with CKD (10-14).

Those studies (10-14) reported that kidney transplantation was a successful in improving pulmonary function of uremic patients. However, data on the effects of kidney transplantation on respiratory muscle strength are limited. Of the aforementioned studies only three assessed changes in respiratory muscle strength after kidney transplant (11, 13, 14). Since survival of CKD patients is increasing with kidney transplantation, it is highly likely for clinicians to face post-kidney transplant patients with complaints about their respiratory function. Therefore, we designed a study to evaluate the effect of kidney transplant on respiratory muscle strength of patients with CKD.

The objective of this study was to compare pre- and post-transplant respiratory muscle strength of patients end stage renal disease (ESRD), who underwent successful kidney transplantation.

MATERIALS AND METHODS

In this cohort study, the population studied consisted of patients aged 15-70 years with ESRD, who were receiving hemodialysis for at least 3 months and were candidates for kidney transplantation. Exclusion criteria included uncontrolled heart disease or arrhythmias, physical activity-limiting musculoskeletal diseases, respiratory and neurologic disorders, cigarette smoking, as well as alcohol, heroin, or opium abuse. The required sample size was calculated to be 26 patients considering $\alpha = 5\%$, $S = 12.5$, $d = 5$, and $Z = 1.96$ within the formula: $N = Z^2S^2/d^2$.

Spirometry was performed 2 days before and 30 days after the operation. The rationale for selecting 30 days was that by this time patients achieve stable status, their urinary catheter is removed, serum creatinine reaches its baseline levels, and dosage of immunosuppressive medications is at their minimum level.

A researcher-designed checklist, which included 3 sections, was used to collect data. In the first section patients' demographic information (age, gender) was filled out. The second segment inquired about the severity of the patients' kidney disease, including duration of hemodialysis, comorbidities (diabetes mellitus, hypertension, anatomic disorders), and medications taken by the patients (e.g., corticosteroids, and erythropoietin). In the third part spirometry data were collected. Respiratory muscle strength is the force of the muscles involved in respiration. P_{IMAX} (maximal inspiratory pressure, MIP) at the mouth measured using the lung residual volume (RV) and P_{EMAX} (maximal **expiratory** pressures, MEP) at the mouth measured by using the total ling capacity (TLC) were used as indicators of respiratory muscle strength. Lower limit normal (LLN) for P_{IMAX} in the age range of 20-54 years is 80 cmH_2O in males and 55 cmH_2O in females. Lower limit normal for P_{EMAX} are 149 and 98 cmH_2O in males and females, respectively. Other laboratory data (blood urea nitrogen, creatinine, sodium, potassium, calcium, phosphorus, and hemoglobin), as well as cyclosporine and corticosteroid dosages administered after transplantation operation were also collected.

Statistical analyses

Descriptive indices including mean and standard deviation (SD), frequency, and percentages were used to report data. Paired t-test was used to compare pre- and post-transplant data. In order to compare P_{IMAX} and P_{EMAX} values between the two groups at two time points (i.e., before renal transplantation and 30 days after the transplantation), student t test or the Mann-Whitney tests was used. Statistical significance was set at p = 0.05. All analyses were performed using SPSS version 20.0

Ethics

The study protocol was approved by the ethics committee of our university. The study details were explained the patients and if they agreed to participate, written informed consent was obtained.

RESULTS

There were 18 males (69.2%). Sixteen patients (61.5%) were younger than 40 years. Hypertension was the most common comorbidity, present in 17 patients (65.4%), followed by kidney anomaly in 6 patients (23.1%), and diabetes mellitus in 5 patients (19.2%). Mean duration of hemodialysis was 18.2 months.

Table 1 presents laboratory parameters assayed before and after kidney transplantation. There were significant decreases in BUN, creatinine, and phosphorus levels after renal transplantation while hemoglobin levels increased significantly afterwards.

Table 2 presents P_{IMAX} and P_{EMAX} measurements before and after kidney transplantation. There were statistically significant increases in both P_{IMAX} and P_{EMAX} measurements after kidney transplantation.

Nineteen patients (73.1%) showed increase in P_{IMAX} and P_{EMAX} values (group 1) while 7 patients (26.9%) did not have any increase in their P_{IMAX} and P_{EMAX} values after kidney transplantation (group 2). Mean (SD) age in groups 1 and 2 were 35.89 (11.07) and 49 (17.51) years, respectively (P = 0.07). Table 3 shows comparison of P_{IMAX} and P_{EMAX} values between the two aforementioned groups before and after kidney transplantation. There was no significant difference in P_{IMAX} and P_{EMAX} values between the two groups before kidney transplantation. However after kidney transplantation P_{IMAX} and P_{EMAX} values were significantly higher in group 1. Likewise, Table 4 compares laboratory data before and after kidney transplantation between groups 1 and 2. Compared to group 2, patients in group 1 had significantly lower phosphorous levels before- and higher hemoglobin levels after undergoing kidney transplantation. Table 5 shows hemodialysis duration, serum cyclosporine level, erythropoietin dosage, as well as corticosteroid dosage for both groups.

Table 1. Comparison of mean (±SD) laboratory data 2 days before and 30 days after renal transplantation

	Before renal transplantation	After renal transplantation	P value
Blood urea nitrogen (BUN)	103.35 (±32.98)	38.65 (±8.08)	< 0.001
Creatinine	6.94 (±2.68)	1.32 (±0.29)	< 0.001
Sodium	139.92 (±1.64)	136.92 (±1.91)	0.07
Potassium	4.7 (±0.75)	4.16 (±0.39)	0.6
Calcium	8.57 (±1)	8.64 (±0.45)	0.36
Phosphorus	5.02 (±1.42)	2.94 (±0.57)	0.001
Hemoglobin	9.95 (±1.56)	11.12 (±2.6)	0.001

P values were obtained by the paired t-test.

Table 2. Comparison of mean (SD) P_{IMAX} and P_{EMAX} measurements before and after renal transplantation

	Before renal transplantation	After renal transplantation	P value	R
P_{IMAX}, cmH_2O	31.88 (±8.58); range= 17-52%	37.65 (±13.39); range= 15-63%	< 0.001	0.71
P_{EMAX}, cmH_2O	33.04 (±16.12); range= 7-77%	39.19 (±20.34); range= 4-80%	< 0.001	0.9

P values were obtained by the paired t-test.

Table 3. Comparison between group 1 (significant increase in P_{IMAX} and P_{EMAX} values after renal transplantation) and group 2 (no increase in the spirometry values)

		Before renal transplantation	P value	After renal transplantation	P value
P_{IMAX}, cmH_2O	Group 1	33.89 (±8.71)	0.33	42.05 (±11.21)	< 0.001
	Group 2	29.14 (±8.19)		23 (±5.29)	
P_{EMAX}, cmH_2O	Group 1	37 (±16.67)	0.07	46.63 (±18.43)	0.001
	Group 2	34.29 (±8.09)		29 (±7.37)	

All values are expressed as mean (±SD).

Table 4. Comparison between group 1 (significant increase in P_{IMAX} and P_{EMAX} values after renal transplantation) and group 2 (no increase in the spirometry values)

		Before transplantation	P value	After transplantation	P value
BUN, mg/dL	Group 1	107.47 (24.56)	0.3	38.32 (6.91)	0.82
	Group 2	92.14 (27.36)		39.57 (11.31)	
Creatinine, mg/dL	Group 1	7.06 (2.68)	0.73	1.29 (0.23)	0.69
	Group 2	6.62 (2.86)		1.4 (0.43)	
Calcium, mg/dL	Group 1	8.5 (1.05)	0.61	8.68 (0.49)	0.53
	Group 2	8.78 (0.88)		8.52 (0.29)	
Phosphorus, mg/dL	Group 1	4.82 (1.29)	0.02	2.91 (0.6)	0.57
	Group 2	6.2 (1.36)		3 (0.49)	
Sodium, mg/dL	Group 1	140.26 (1.72)	0.3	137.21 (1.9)	0.22
	Group 2	139 (1)		136.14 (1.84)	
Potassium, mg/dL	Group 1	4.56 (0.66)	0.07	4.16 (0.39)	0.69
	Group 2	5.07 (0.89)		4 (0.41)	
Hemoglobin, g/L	Group 1	9.93 (1.75)	0.73	11.55 (2.95)	0.02
	Group 2	10 (0.97)		10.28 (0.85)	

All values are expressed as mean (±SD).

Table 5. Comparison of mean (SD) hemodialysis duration, serum cyclosporine level, erythropoietin and corticosteroid dosages between group 1 (significant increase in P_{IMAX} and P_{EMAX} values after renal transplantation) and group 2 (no increase in the indices)

	Group 1	Group 2	P value
Hemodialysis duration (month)	13.37 (±6.73)	23.14 (±10.83)	0.56
Serum cyclosporine level	239.42 (±74.68)	324 (±115.52)	0.1
Erythropoietin dosage	6631.58 (±3130.68)	7428.58 (±2598.94)	0.61
Corticosteroid dosage	24.74 (±3.89)	26.43 (±4.75)	0.42

DISCUSSION

In agreement with previous studies (2-4), our patients had low P_{IMAX} and P_{EMAX} values. Both P_{IMAX} and P_{EMAX} values increased significantly after 30 days post-kidney transplantation. However, even after 30 days post-transplantation these values were lower than the LLN.

P_{IMAX} and P_{EMAX} are regarded as the best indicators of respiratory muscles strength. These indices can be measured non-invasively at bedside and are widely used to predict clinical outcomes. P_{IMAX} reflects the strength of the diaphragm and other inspiratory muscles. P_{EMAX} reflects the strength of expiratory muscles. In adults, P_{IMAX} values of more than 80 cmH_2O and P_{EMAX} values of more than 90 cmH_2O exclude respiratory muscle weakness. When these values are less than 60 cmH_2O they indicate respiratory muscle weakness (15, 16). Our results are compatible with those of other similar studies. Guleria et al. (11) studied 29 patients with mean kidney disease duration of 13 months and reported that mean (SD) P_{IMAX} increased from pre-kidney transplantation value of 101.8 (37.58) to 140.48 (43.3) on day 30 and to 101.08 (37.58) cmH_2O on post-op day 90. Likewise, mean (SD) P_{EMAX} increased from baseline value of 98.55 (30.03) to 122.27 (34.05) on post-op day 30 and to 122.55 (37.37) cmH_2O on post-op day 90. Mean hemodialysis duration in our patients was longer than those reported by other groups (18 months vs. 13 months, respectively). This might partly explain the difference between baseline P_{IMAX} and P_{EMAX} values between our patients and those reported by Guleria et al. (11). Other parameters like spirometry protocol, age, and sex may have played a role in this discrepancy and we cannot compare all of them. Also, they followed their patients for 90 days (11) while we followed ours for 30 days. It is possible to obtain even higher P_{IMAX} and P_{EMAX} measurements with longer follow-ups. Therefore, it could be a recommended for future studies to design a longitudinal cohort and follow the patients for longer periods in order to find out whether over time these measurements improve or remain unchanged.

Bush and Gabriel (13) also reported significantly higher peak inspiratory flow (PIF) (93.6% vs. 78.7% of predicted normal) and peak expiratory flow (PEF) (89.5% vs. 84.3% of predicted normal) values in post-renal transplantation patients when compared to hemodialysis cases. In a study by Cury et al. (14), post-kidney transplant patients had higher P_{IMAX} values (87 cmH_2O) compared to patients on hemodialysis (67.19 cmH_2O). This was also true for P_{EMAX} values (89.2 vs. 76.2 cmH_2O). They suggested that even after kidney transplantation, the patients did not gain full respiratory muscle strength. This is in line with what we observed in our study; patients continued to suffer from significant respiratory muscle weakness despite resolution of uremia (BUN and creatinine decreased and reached normal levels after transplantation) However, other studies suggest that this pattern of increased P_{IMAX} and P_{EMAX} is not necessarily always seen after renal transplantation. Karacan et al. (17) compared P_{IMAX} between post-renal transplantation and hemodialysis/peritoneal dialysis patients and found that P_{IMAX} decreased in all three groups. They suggested that long-term immunosuppressant therapy, such as corticosteroid therapy after kidney transplantation can explain decreased P_{IMAX} and P_{EMAX} in such patients. We compared the required corticosteroid dosage between those with significant increase in P_{IMAX} and P_{EMAX} vs. those who did not have such increases and found no statistically significant difference. Therefore we think that factors other than corticosteroid therapy may explain these findings, though we cannot fully excludes the possibility of corticosteroid interference with respiratory muscle strength.

Despite numerous previous studies the topic of respiratory muscle weakness in CKD patients and the role of kidney transplantation are not fully understood. In future studies factors such as duration of hemodialysis dependence and its effect on respiratory muscle strength and possibility of its correction after operation should be considered. Also, other factors such as respiratory rehabilitation, immunosuppressant therapy, and other medications administered after kidney transplantation should be investigate to explain respiratory muscle weakness in dialysis dependent patients.

CONCLUSION

Patients with CKD on hemodialysis for a mean period of 18 months had considerable limitation of their respiratory muscle function. Although kidney transplantation resulted in significant increase in P_{IMAX} and P_{EMAX} measurements by post-op day 30, these were still lower than the LLN. This shows that kidney transplantation may not result in full recovery of respiratory muscle strength in hemodialysis dependent patients and factors other than uremic myopathy may contribute to their respiratory muscle weakness.

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