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Effect of Intradialytic cycling exercise on 2 minutes walking test and VO₂max in chronic kidney disease patients

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Abstract---Patients with end stage CKD are characterized by low levels of physical activity and ongoing decline in physical function, especially with routine hemodialysis (HD). Physical inactivity significantly increases the risk of morbidity and mortality in patients with HD. Two Minute Walking Test (2MWT) and VO₂ max are parameters that can be used to evaluate functional capacity and cardiopulmonary fitness. Exercise can improve cardiovascular ability, dialysis effectiveness, physical function, and health-related quality of life in patients undergoing HD. This study aimed to investigate the effect of intradialytic cycling exercise on the 2MWT and VO₂max in CKD patients undergoing hemodialysis. Thirty CKD patients participated in this study. From the total, 4 subjects dropped out, leaving twenty-six CKD patients. Subjects divided into exercise and control groups were

able to follow the study until the end. The exercise group did a low-intensity intradialytic cycling exercise program for 12 weeks. Both groups were given education about physical function and cardiopulmonary fitness in CKD patients and continued drug therapy and diet as before. 2MWT and VO₂max were evaluated before and after the intervention. There was an improvement in 2MWT and VO₂max after intervention in the exercise group (2MWT $p = 0.002$ and VO₂max $p = 0.002$) which was not found in the control group (2MWT $p = 0.102$ and VO₂max $p = 0.102$). 12 weeks of intradialytic cycling exercise improved the physical function in CKD patients as evidenced by a significant increase in 2MWT and VO₂max.

Keywords---hemodialysis, chronic kidney disease, rehabilitation, intradialytic cycling exercise, 2 minute walking test, VO₂max.

Introduction

Chronic Kidney Disease (CKD) tend to have many comorbidities, especially cardiovascular disease, and mineral and bone disorders. Inflammation, endothelial dysfunction, and impaired bone mineralization are important factors that contribute to morbidity and mortality in hemodialysis patients. Lack of physical activity causes chronic inflammation and wasted protein and energy (Liao et al., 2016). CKD are characterized by low levels of physical activity and ongoing decline in physical function, especially with routine hemodialysis (HD), their physical activity levels can reach 20%-50% lower than normal population (Anding et al., 2015), (Sawant et al., 2014). Physical inactivity significantly increases the risk of morbidity and mortality in patients with HD. HD patients often have decreased quality of life and physical function. Meanwhile, an increase in the level of physical function and physical activity itself is associated with a decrease in morbidity, hospitalization rates and an increase in the quality of life of patients with HD (Greenwood & Koufaki, 2017).

Based on WHO data in 2015, it was estimated that 1.2 million people died worldwide due to kidney failure, a fairly large increase of around 35 percent compared to 2005. Meanwhile, in 2010, it was estimated that there were 2.3 to 7.1 million people. people died due to chronic kidney failure who did not get access to dialysis therapy. Overall, it is estimated that as many as 5-10 million people die each year due to kidney failure (Luyckx et al., 2017). Data from the dialysis unit of Dr Soetomo Hospital Surabaya shows an increase in patients who routinely undergo routine hemodialysis twice a week in the last three years; 245 patients in 2013, 255 patients in 2014 and 303 patients in 2016 (Farida et al., 2018).

Exercise prevents the side effects of cardiovascular inactivity and mortality. In recent developments, exercise can improve cardiovascular ability, dialysis effectiveness, physical function, and health-related quality of life in patients undergoing HD. Intradialytic exercise has more benefits than interdialytic exercise, namely fewer patients drop out, higher motivation, safer, and structured training with close monitoring, saving time because patients do not have to attend

additional training sessions and increasing the effectiveness of dialysis (Anding et al., 2015), (Liao et al., 2016). Physical performance and functional balance of CKD patients who were given exercise therapy also improved significantly, marked by an increase in the 6 minutes walking test and the Berg balance scale test (Abdelaal & Abdulaziz, 2019). Exercise can also increase oxygen-carrying capacity and exercise tolerance in CKD patients (Elmonem et al., 2019).

Measurement or monitoring using VO₂ max is the parameter most often used to evaluate a person's functional capacity, and as a predictor of life expectancy in CKD patients. The Six Minute Walking Test has proven to be a good tool for evaluating functional capacity and has been widely used in patients with chronic disease, but has limitations in its use in untrained subject. The 6-minute (6MWT) walking test is too tiring, takes longer and increases the risk of falling, so the 2-minute (2MWT) walking test may be an alternative (Kohl et al., 2012), (Pratiwi, 2019). The objective of this study was to prove intradialytic cycling exercise can affect 2 minutes walking test and VO₂ max in regularly HD patients in Dr. Soetomo Hospital.

Methods

Study design

This research was performed from March to June 2021 with study design was a quasi-experimental method with a pre-test and post-test randomized control group. All recruitment, sampling of blood, and intervention during the study were conducted at Hemodialysis Unit Dr. Soetomo Hospital.

Sampling method

Recruitment began in March 2021, the research subjects were Chronic Kidney Disease patients who treated hemodialysis regular at the Hemodialysis Unit Dr. Soetomo Hospital. Subjects were selected with consecutive sampling to reach a minimum sample size of 30 subjects. Sample size was determined by hypothesis testing using formula for difference in means. The inclusion criteria was age 20-50 years, perform routinely hemodialysis for minimum 3 months, systolic blood pressure (SBP) 110-180 mmHg, and diastolic 70-90 mmHg, and willing to participate in this research voluntarily with signed a consent form to be a research subject.

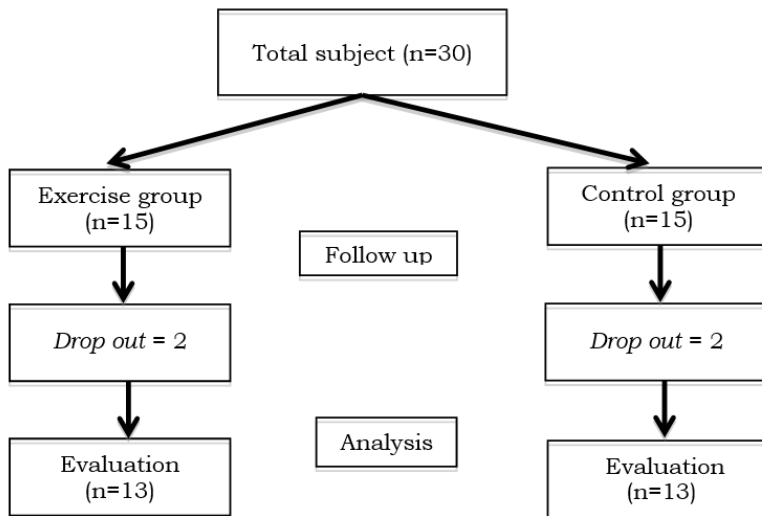


Figure 1. Subject Recruitment

The exclusion criteria was performing a routinely aerobic exercise program twice a week, ischemic heart disease, malignant arrhythmia, heart failure New York Heart Association classification class III and IV, suspicion of new stroke, hemoglobin less than 8 mg/dL, any of erythema, wound, ulcers or gangrene in either or both lower extremity, limitation on range of motion of knee joint more than 45° of flexion, 10° of extension, and 45° of hip flexion, neuromusculoskeletal disease of the lower limbs that disturb ambulation, unable to ambulate independently, uncontrolled hyperglycemia (random blood glucose > 250 mg/dL), cognitive dysfunction (MoCA < 18), severe visual impairment, COVID-19 patients with or without symptoms (using the "Skoring for Skrinig Corona Virus Disease (COVID-19) - RSUD Dr. Soetomo, 2020" sheet).

The drop out criteria were subjects who refused to continue the study for any reason, couldn't complete exercise based on research protocol, 2 or more absences of consecutive training, or total absences were more than 20% presence (maximum of three times) absent from exercise and hospitalization.

Intervention

Subjects were randomly divided into two groups: first group that performed no exercise (control group) and second group that performed intradialytic cycling exercise (exercise group). The intervention group received a mild intensity intradialytic cycling exercise program (Target Heart Rate = HR rest + 30-39% HRR or 11-12 Borg scale) with a cycle ergometer (Terra Fitness®) fixed on the footrest of the patient's bed. Measurement of heart rate reserved (HRR) by using formula of Karvonen, $HRR = 220 - \text{age} - \text{HR rest}$ (Riebe, Deborah., Ehrman, Jonathan K., Liguori, Gary., Magal, 2018). The exercise was performed during the first 2 hours of HD for 30 minutes consisting of 5 minutes of warm-up, 20 minutes of core phase

and 5 minutes of cooling down. Random blood glucose was measured using Nesco-Multicheck® before the exercise in subject with diabetes mellitus. The frequency of exercise was twice a week based on hemodialysis schedule and was performed until twelve weeks. Both groups were given consent about the cardiopulmonary fitness and continued drug therapy and diet as before.

Outcome measures

The parameters that were evaluated in this study were Two Minute Walking Test (2MWT) and VO₂ max which were evaluated twice, before the aerobic exercise program, and at the end of the study after 12 weeks of the aerobic exercise program intervention. Two minutes walking test is the distance (in meters) traveled by subject walking as far as possible can be done in 2 minutes.

VO₂ max is maximum aerobic capacity (in mL/kg/minute) which describes the maximum amount of oxygen consumed per unit time by a subject during exercise which is getting heavier until the fatigue phase (Smirmaul et al., 2013). VO₂ max was measured using formula from distance traveled by subject when performed 2MWT (Pratiwi et al., 2019).

Data analysis

The statistical distribution of the data was analyzed using the Shapiro Wilk. Descriptive statistics were used to calculate the mean and standard deviation. Demographic data and initial assessment results were compared with t-tests using the Statistical Package for the Social Sciences for Windows version 25 (SPSS Inc., Chicago, IL, USA). Mann Whitney test used to perform to compare the post-test results between groups. Wilcoxon test was used to compare the differences between pre and post intervention results in the exercise group. Paired t-test was used to compare the differences between pre and post observation results in the control group. $P < 0.05$ was statistically significant.

Results

Total subject was 30 patients who met the inclusion criteria and did not include the exclusion criteria. Subjects were divided into 2 groups, consisting of 15 subjects in each group. Of the 30 patients, there were 4 patients who dropped out due to illness requiring treatment and withdrew from the study for personal reasons, so there were 26 patients were able to continue the study.

There were 2 subjects who experience complaints due to exercise, 1 subject complaining of muscle pain and 1 other subject complaining of post-exercise dizziness. Dizziness and muscle cramps were also reported by subjects in control group. One of the subjects in the intervention group complaints of shortness of breath which required treatment in the room so he was dropped out. The complaint of shortness of breath occurred 2 days after the training session so it was categorized as not including exercise side effects. One patient in the control group who complained of dizziness and shortness of breath unrelated to the study and

required treatment in the emergency department was excluded from the study. There were no reported adverse events related to COVID 19 in this study.

Table 1. Baseline Characteristic of the subject

Characteristics	exercise		control	
	Mean±SD	p	Mean±SD	p
Age	39,62±6,31	0,859	36,85±4,99	0,167
BMI	23,36±4,44	0,261	22,31±3,06	0,680
Hb	11,12±1,32	0,017	9,48±1,27	0,283
Alb	3,54±0,16	0,476	3,32±0,18	0,085
Blood glucose	118,85±26,1	0,178	112,23±15,11	0,113
MoCa	5	0,076	24,77±2,42	0,048
	24.62±3.38			

Characteristics	Total n=26	Group		p
		Exercise (n=13)	Control (n=13)	
Gender				
Men	15(57,69%)	7(53,84%)	8(61,53%)	-
Women	11(42,30%)	6(46,15%)	5(38,46%)	-
Age (years)	38,23±5,75	39,62±6,31	36,85±4,99	0,157
BMI (kg/m ²)	22,84±3,77	23,36±4,44	22,31±3,06	0,83
Comorbid				
Hipertension	22 (84,62%)	11 (84,62%)	11 (84,62%)	-
DM	2 (7,69%)	1 (7,69%)	1 (7,69%)	-
Urolithiasis	3 (11,53%)	2 (15,38%)	1 (7,69%)	-
Drugs				
CCB	18 (69,23%)	10 (76,92%)	8 (61,54%)	-
B bloker	8 (30,77%)	2 (15,38%)	6 (46,15%)	-
ARB	3 (11,54%)	2 (15,38%)	1 (7,69%)	-
Methyldopa	1 (3,85%)	0 (0%)	1 (7,69%)	-
Allopurinol	4 (15,38%)	3 (18,75%)	1 (7,69%)	-
Simvastatin	2 (7,69%)	2 (15,38%)	0 (0%)	-
Suplemen Ca	7 (26,92%)	3 (18,75%)	4 (30,77%)	-
Suplemen Fe	4 (15,38%)	3 (18,75%)	1 (7,69%)	-
Asam Folat	6 (23,08%)	2 (15,38%)	4 (30,77%)	-
Furosemid	1 (3,85%)	1 (7,69%)	0 (0%)	-
Vit B	2 (7,69%)	2 (15,38%)	0 (0%)	-
Onset of HD				
0-3 years	9 (34,62%)	5 (38,46%)	4 (30,77%)	-
>3 years	17 (65,38%)	8 (61,54%)	9 (69,23%)	-
Duration of HD				
4,5 hour	17 (65,38%)	9 (69,23%)	8 (57,14%)	-
5 hour	9 (34,62%)	4 (30,77%)	5 (38,46%)	-

There were 15 men and 11 women in this study. The mean age of the subjects was 39.62 ± 6.31 years in the exercise group and 36.85 ± 4.99 years in the control group. There was no significant difference in the distribution of age data between groups ($p = 0.157$). BMI in the exercise group was 23.36 ± 4.44 kg/m², while the

Table 2. 2MWT and VO₂ max between group

Variable	Pre Intervention			Post Intervention		
	CG (n=13)	EG (n=13)	p-value	CG (n=13)	EG (n=13)	p-value
2MWT (m)	102,05±15,35	100,68±21,64	0.980	108,39±13,54	134,83±21,59	0.001*
VO ₂ max (mL/kg/min)	19,98±5,91	18,31±8,40	0.564	21,48±5,37	31,80±19,98	0.106

2MWT: 2 Minute Walking Test, s: seconds, EG: exercise group, CC: control group

*Significant difference if $p\text{-value} < 0,05$

Table 3. 2MWT and VO₂max within group

Variable	CG (n=13)			EG (n=13)		
	Pre	Post	p-value	Pre	Post	p-value
2MWT (m)	102,05±15,35	108,39±13,54	0.102	100,68±21,64	134,83±21,59	0.002*
VO ₂ max (mL/kg/min)	19,98±5,91	21,48±5,37	0.102	18,31±8,40	31,80±19,98	0.002*

2MWT: 2 Minute Walking Test, s: seconds, EG: exercise group, CC: control group

*Significant difference if $p\text{-value} < 0,05$

control group was 22.31 ± 3.06 kg/m². There was no significant difference in the distribution of BMI between the exercise and control groups ($p=0.83$).

The results of the homogeneity test of 2MWT was no significant difference between the exercise group and the control group before the intervention with a p value of 0.853, which means that the two groups are homogeneous. The results of the homogeneity test on VO₂max showed no significant difference between the treatment group and the control group before the intervention was carried out with a p value of 0.904 which indicates that the data is homogeneous.

The results of the Mann Whitney test showed that there was no significant difference between 2MWT before intervention in the exercise group and the control group with a p value of 0.980. The results of the independent t test of VO₂max before the intervention in the exercise and control groups showed no significant difference between the two groups with a p value of 0.564.

The results of the Mann Whitney test showed that there was a significant difference of 2MWT after the intervention in the exercise group and the control group. The mean of 2MWT after the intervention in the exercise group was 134.83 ± 21.59

meters, while the control group obtained an average of 108.39 ± 13.54 meters with a p value of 0.001.

The results of the Mann Whitney test showed that there was no significant difference in VO₂max after the intervention in the exercise group and the control group. The mean VO₂max after the intervention in the treatment group was 31.80 ± 19.98 mL/kg/min, while the control group obtained an average of 21.48 ± 5.37 mL/kg/min with a p value of 0.106

Wilcoxon test results show that there is a significant difference of 2MWT before and after intervention in the exercise group. There was an increase in the average 2MWT before the intervention from 100.68 ± 21.64 meters to 134.83 ± 21.59 meters with a p-value of 0.002. Effect size is calculated using Cohen's d formula with the result 1.57 (large effect size).

There was an increase in the average of VO₂max before compared with after the intervention from 18.31 ± 8.40 mL/kg/min to 31.80 ± 19.98 mL/kg/min. The results of the Wilcoxon test showed that there was a significant difference in VO₂max before and after the intervention in the exercise group with a p-value of 0.002. Effect size is calculated using Cohen's d formula with the result 0.88 (large effect size)

There is an increase in the average 2MWT from 102.05 ± 15.35 meters to 108.39 ± 13.54 meters. Paired t-test results showed that there was no significant difference of 2MWT before and after intervention in the control group with a p-value of 0.102. There was an increase in the mean VO₂max from 19.98 ± 5.91 mL/kg/min to 21.48 ± 5.37 mL/kg/min. Paired t test results showed that there was no significant difference in VO₂max before and after intervention in the control group with a p-value of 0.102.

Discussion

Patients with advanced stage renal failure tend to have many comorbidities, especially cardiovascular disease, and mineral and bone disorders. Inflammation, endothelial dysfunction, and impaired bone mineralization are important factors that contribute to morbidity and mortality in hemodialysis patients. Lack of physical activity causes chronic inflammation and wasted protein and energy (Liao et al., 2016).

The results of this study showed an average increase of 2MWT from 100.68 ± 21.64 meters before the intervention to 134.83 ± 21.59 meters after the intervention. Intradialytic cycling exercise for 12 weeks has significantly increased 2MWT with a large effect size. The results of this study are in line with research by Hristea et al which reported a significant increase in the 6-minute walking test by 22% in the group given intradialytic cycling exercise for 6 months (Hristea et al., 2016). The study of Groussard et al also reported a significant increase of 6MWT by 23.4% in the group given intradialytic cycling exercise 3 times a week for 3 months (Groussard et al., 2015). Wu et al also reported an increase in mileage in a 6-minute walk test of patients given intradialytic cycling 3 times a week for 12 weeks. This

study proves that intradialytic cycling exercises can increase the distance traveled on the walking test, which indicates that the functional capacity in the exercise group increased significantly than before (Wu et al., 2014).

There was an increase in the average VO₂max from 18.31±8.40 mL/kg/min before the intervention to 31.80±19.98 mL/kg/min after the intervention. The increase in VO₂ max after the intervention in the exercise group has statistically significant with a fairly large effect size as well. VO₂max at the age of 30-39 years is divided into 6 categories, namely very low, low, adequate, good, very good and superior. Men and women have slightly different values. The mean baseline VO₂max in this study was not categorized as normal, or below very low (19-22.5 mL/kg/min for women and 27.2-32.7 mL/kg/min for men) at age 30-39 years. After the intervention, the mean value of VO₂max increased to enter the 3 categories above, which is sufficient (28.2-31.2 mL/kg/min for women) and increased by 1 category for men aged 30-39 years which is very low (27.2 -32.7 mL/kg/min) (Riebe et al., 2018).

At the beginning of the study, the 2MWT in the treatment group and the control group did not differ significantly with a p value of 0.980, and a homogeneity test was carried out which showed that the data were homogeneous before the intervention. At the end of the study, it was found that the exercise group 2MWT increased significantly (p=0.002), while the control group not significant (p=0.102). Two Minutes Walking Test the exercise group got better than the control group after intervention.

VO₂max in the exercise and control groups at the beginning of the study was not significantly different (p=0.564). At the end of the study, the VO₂max of the exercise group increased significantly (p=0.002), but it was not significant in the control group (p=0.102). The VO₂max of the exercise group was better than the control group after the intervention. In a study conducted by Ouzouni et al, VO₂max in HD patients who were given intradialytic exercise increased from 20.9(5.4) to 25.3(5.3) p<0.05. In a 2014 study conducted by Bohm et al, the VO₂max of HD patients given intradialytic cycling exercise increased from 18.2 (8.2) to 20.0 (8.2) at 12 weeks (Bohm et al., 2014), (Ouzouni et al., 2008). These two studies show that the baseline VO₂max in HD patients < 21, is very different from the VO₂max in normal sedentary people, which ranges from 27-30 in women, 35-40 in men (Capritto, 2019).

Endurance exercise in CKD patients has shown an increase in physical function (aerobic capacity) and quality of life. Endurance training has also been shown to improve muscle strength and physical function in patients hemodialysis. In recent developments, exercise can improve cardiovascular outcomes such as blood pressure and lipid profile, dialysis effectiveness, physical function, health-related quality of life in patients undergoing HD (Anding et al., 2015), (Liao et al., 2016). Huang et al recommend aerobic exercise or combination exercise performed during hemodialysis to increase VO₂max. Low-intensity aerobic exercise intra hemodialysis for 6 months is reported to increase the efficacy of dialysis and physical performance (Cheema et al., 2007).

This study proves that low-intensity intradialytic exercise for 12 weeks can increase cardiopulmonary capacity and fitness by increasing 2MWT and VO₂max through mechanisms of minimizing inflammation, increasing anabolic pathways and cardiac response to exercise. Exercise in dialysis patients can increase anabolism by stimulating intracellular anabolic signaling pathways and producing protein balance. Aerobic exercise carried out for a long time can detect an increase in the number of type 1 muscles (Cheema et al., 2007). Long-term physical exercise causes a response to the heart in the form of a decrease in heart rate (heart rate), but stroke volume is more efficient, so that cardiac output also increases. Blood circulation is getting better so that oxygen transport be good. This causes oxygen uptake to also increase so that it can increase VO₂max. Through this mechanism, cardiopulmonary capacity and fitness in HD patients who tend to be low can be increased, either directly increasing their VO₂max or by preventing muscle wasting complications that cause muscle disuse so that their functional capacity decrease.

Limitation

This study has several limitation, including several confounding variables that cannot be controlled such as age, BMI, fat mass, drugs, diet, comorbidities that can affect the 2MWT and VO₂max variables in this study. The second is exercise intensity that has not been maximized is prescribed because it is difficult to achieve the intensity according to the target heart rate in the early months of training (the Borg scale is first achieved).

Conclusion

Intradialytic aerobic cycling exercise can improve functional capacity and cardiopulmonary fitness in chronic kidney disease patients undergoing regular hemodialysis which can be seen with an increase of 2MWT and VO₂max. Considering that CKD patients undergoing regular HD are a vulnerable population, serious adverse events, although not related to exercise intervention, can occur in intradialytic exercises, so that strict screening and adequate education before exercise and supervision during exercise are very necessary.

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Conflict of Interest

The authors declared no conflict of interest.

Author Contribution

All authors equally contributed to preparing this article.

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