# Intradialytic Neuromuscular Electrical Stimulation versus Cycling on Renin Hormone in Chronic Kidney Disease

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**Abstract**

**Background**: Worldwide accelerated advances in physical rehabilitation of chronic kidney disease; particularly whom undergoing haemodialysis. Multimodal therapeutic approaches may maximize their recovery through preliminary evidence indicating both intradialytic neuromuscular electrical stimulation or cycling exercise might permit obvious benefits. **Purpose:** To investigate the effect of intradialytic neuromuscular electrical stimulation and cycling on renin hormone levels in patients with chronic kidney disease. **Materials & Methods:** A single prospective clinical, randomized control trial. Sixty participants of both genders with chronic kidney disease whom undergoing haemodialysis three times per week from ElQnatar Hospital, Qalyobia, Egypt. They were randomly allocated into two equal groups; Group A 30 subject received intradialytic neuromuscular electrical stimulation protocol; 3 session per week for eight weeks; and Group B 30 subject received intradialytic cycling exercise protocol for up to one hour per session; 3 session per week for eight weeks. Evaluation involving renin hormone test, leg musculature strength using dynamometer, kidney function test and frequency and number of sessions per month. Statistical analysis with significance level 0.05 level. **Results:** Unsignificant differs revealed at baseline analysis. Both groups had revealed a significant decrease in renin hormone test reported values, and a significant increase in leg musculature strength, and kidney function test values, and frequency and number of sessions per month reported values post treatment. As well, there was significant improvement in group B compared with group A post treatment in term of renin hormone test values, leg musculatures` strength, frequency and number of sessions per month, as well kidney function test. **Conclusions:** It can be concluded that application of intradialytic cycling exercise protocol and/ or intradialytic neuromuscular electrical stimulation protocol are valuable for managing chronic kidney disease whom undergoing haemodialysis patients, with superiority for intradialytic cycling exercise protocol in terms of renin hormone test values, leg musculatures` strength, frequency and number of sessions per month, as well kidney function test. therefore, could be recommended intradialytic cycling exercise protocol for chronic kidney disease whom undergoing haemodialysis patients' management.

**Key words: Chronic kidney disease, Dynamometer, Intradialytic cycling, Intradialytic neuromuscular electrical stimulation, Renin hormone test.**

## Introduction

Chronic Kidney Disease (CKD) is a common worldwide known as persistent abnormality kidney function and/or structure such as glomerular filtration rate [GFR] <60 mL/min/1.73 $m^2$ or albuminuria ≥30 mg per 24 hours for more than three months. It is frequently unrecognized and often exists together with other comorbidities. (1) Up to date, preservation of kidney function could improve outcomes and permitted through non-pharmacological strategies and chronic kidney disease-targeted, as well kidney disease-specific pharmacological interventions. (2)

Recent update of classification of CKD has evolved over time into defined five stages and uses combination of an index of kidney function, GFR and markers of renal damage to define actual patient`s stages. Optimal management of CKD includes cardiovascular risk reduction, treatment of albuminuria, also avoidance of potential nephrotoxins and adjustments to drug dosing. Plus, CKD patients require monitoring for suspected complications i.e., hyperkaliemia, metabolic acidosis, hyperphosphatemia, secondary hyperparathyroidism and anemia. (3)

Renin, a hormone secreted by the kidney, plays a crucial role in regulating blood pressure and fluid balance in the body. In patients with CKD, the renin-angiotensin system (RAS) is overactive leading to hypertension and other complications. (4). Regular low- to moderate-intensity aerobic exercise - a sequence of bodily movement developed by the repeated contraction of skeletal muscle group(5). High intenisty interval training improve functional capacity(6)

Meta-analytical evidence indicates that neuromuscular electrical stimulation (NMES) is an effective strategy against muscle weakness in CKD patients at high risk such as critically ill patients or adults with advanced disorders. (7) NMES along 30 to 60 minutes, three times per week has been proven to improve muscle strength and functionality in different clinical situations, such as pre-frail and long-stay hospitalized elderly. [8]

Aerobic exercise has been shown to have beneficial effects on the health of patients with CKD including improving cardiovascular function, reducing inflammation, and improving quality of life. [9] Intradialytic cycling, a type of aerobic exercise performed during haemodialysis, has been shown to be effective in improving physical function and reducing cardiovascular risk factors in patients with CKD. [10]

Although great advances in management of chronic kidney disease (CDK), unless CDK remains a critical health challenge. An annual increase in CDK by 5-6% makes it obvious issue across every country, by the last decade across worldwide not Mediterranean region only. [11] Thus, the main objective of current study is an attempt to investigate the effect of intradialytic neuromuscular electrical stimulation and cycling on renin hormone levels in patients with chronic kidney disease.

**Material and Methods:**

A single prospective clinical, randomized control trial was conducted on sixty participants of both genders with CKD selected from ELQNATAR hospital, Qalyobia Governorate, Egypt. Prior to initiating the study, each participant was signed a consent form before participation in the study. The investigation was carried out in accordance with the ethical standards specified in the 1964 Declaration of Helsinki and received approval from the Research Ethical Committee at the Faculty of Physical Therapy, Kafrelsheikh University, Egypt (No. P.T.REC /012/005511).

The eligible participants met the following inclusion criteria: age between 50 and 60 years old of both genders, their CKD stage 3-5 classified and undergoing haemodialysis three times per week under full medical supervision.

Patients were excluded if they had any of the following criteria: cardiovascular diseases i.e., recent myocardial infarction, unstable angina or cognitive heart failure; vascular disorders i.e., intermittent claudication; neuromuscular disorders; unstable medical conditions i.e., uncontrolled hypertension, uncontrolled diabetes, or active infection, hepatic disorders, knee arthritis, or inability to perform assigned exercise intervention.

Total sample size was 60 subjects with 30 subjects in each group. Patients were randomly assigned to two equal groups. **Group A** received intradialytic neuromuscular electrical stimulation protocol, for 30 minutes, 3 sessions per week for successive 8 weeks. **Group B** received intradialytic cycling exercise protocol for up to one hour per session, 3 sessions per week for successive 8 weeks.

**Instruments**

**Evaluating instruments:**

**i. Blood analyzer device**

GEM Premier 3000, Werfen Co., 2020, USA device is a complete complex device was been used routine laboratory for assessment of renin hormone level, and kidney function test. It is a valid, reliable and sensitive device that was been calibrated before verified usage.

**ii. Dynamometer**

digital dynamometers (5710e/5715, Takei Scientific Instruments Co. Ltd., Niigata, Japan) has good reliability and excellent validity for assessing proximal musculoskeletal strength. Its measuring range is 0-300 kilogram per force, minimum measurement unit 1 kilogram per force, display on scale plate, with dimensions approximately 315 millimeters width, 315 millimeters depth, and 328 millimeters height, and the total weight approximately 3.7 kilograms including weight of handle. It generally demonstrates good reliability and validity when used under standardized conditions as presented in fig. (1). [12]

**Treatment instruments:**

**i. Portable Chattanooga electric stimulation device**

FDA- approved, Intellect mobile stim unit that manufactured by DJO, LLC, and used for micro-current standard Rehabilitation 4 channels stimulator, and 4 full programs categories. It was automate calibrated before intervention. The device dimensions (138X 95X 33 3m) and 300 grams including battery packed (941213; Nickel metal hydride NiMH, 4.8V2000 mA/h). with constant current up to a resistance of maximum 1300 Ohm/Channel, Maximum pulse intensity 120 mA, pulse width 30-400 µs, as well operating temperature environment 15°-40° C with relative humidity 30-60% as presented in fig. (2).

**ii. Cycling device**

FDA- approved Uten's third-generation appearance design adopts high-grade gray color. It is made of durable steel frame. The 4 anti-slip rubber pads prevent sliding and protect the surface during training. Its LCD screen has 4-function display screen.

**Assessment Procedures**

i. At the **beginning**, all demographic data including age, weight, height, and gender were documented, along with screening outcome measures.

ii. **Renin hormone test& Kidney function test,** Samples from each participant were collected early morning before dialysis at the beginning of the study for both groups (A& B), and after the end of the study. Blood samples were collected by responsible nursing staff from renal vein through the already inserted catheter/ or directly from participant`s veins. [13, 14]

iii. **Cardiorespiratory reserve/ $VO_2$ test** Cardiorespiratory reserve/ $VO_2$ test was measured for all participants in group B, only before the beginning, and after the end of the study. $VO_2$ reserve was measured, while the participants were cycling. with both feet cycling and arms resting naturally at participants` sides. $VO_2$ reserve = $VO_2$ Maximum- Resting $VO_2$ ml/kg/min. Where, Resting $VO_2$ was usually around 3.5 ml/kg/min by targeting the exercise loading around 70% intensity for each participant. The targeted $VO_2$ reserve was been calculated at the same equation. Once the $VO_2$ Maximum was obtained for each participant, the $VO_2$ reserve was calculated by the following equation (Target $VO_2$ = (VO2R multiplied by 70 % of the intensity) + Resting $VO_2$) to calculate the targeted $VO_2$ reserve. [15]

iv. **Leg musculatures` strength evaluation** Bilateral leg musculatures strength evaluation using digital leg dynamometers was measured for all participants before the beginning of the study for both groups (A& B), and after the end of the study. Each participant was seated at the edge of the bed while conducted intradialytic session, while the participants` lower extremities positioned at 90° knee flexion, while the researcher himself applied digital leg dynamometer and ordered the participant to extend his/ her lower extremity. Measurements were repeated three times at intervals of 1-2 minutes. [16, 17]

**Treatment procedure:**

**1. Intradialytic Neuromuscular electrical stimulation protocol for Group (A), only**

Each participant in group (A), has received intradialytic neuromuscular electrical stimulation protocol that was applied bilaterally to quadriceps under direct researcher supervision along 30 minutes for each session, 3 sessions per week over eight conscious weeks after approval of caregivers. Then, each was asked to relaxed supine in comfortable clothes with no metallic objects or any sensitive to magnetic field objects. The portable Chattanooga electric stimulation device has been switched on and adjusted the current amplitude/ strength from 5-140 mA according to each participant`s targeted strength, frequency seated at 5Hz as presented in Fig (3). The intradialytic neuromuscular electrical stimulation was been applied using adhesive electrodes in a neoprene garment, applied bilaterally to the quadriceps using portable Chattanooga electric stimulation device that operated at temperature environment 15°up to 40° C with relative humidity 30-60%. A five-minute warm-up and cool down at a lower frequency (4 Hz) were automatically applied by the stimulator. [18]

**2. Intradialytic cycling exercise protocol for Group (B)**

Each participant in group (B) has received intradialytic cycling exercise protocol whilst seated on a dialysis chair under direct supervision along 45 minutes for each session, 3 sessions per week over four conscious weeks after approval of caregivers. Then, each participant has undergone completed a familiarization period, progressing to at least 30 minutes of exercise protocol. Thereafter, cycling was performed for up to one hour per session (minimum of 50 minutes), initially at a workload (Watts) equivalent to that achieved at 40- 60% $VO_2$ reserve. Exercise intensity was regulated using heart rate and rating of perceived exertion (RPE). as presented in figure (4). A five-minute warm-up and cool down were performed at each session, with an extended cool down advised where a risk of post-exercise hypotension was identified. [19,20].

**Statistical analysis**

Unpaired t-test was conducted for comparison of subject characteristics between groups. Chi squared test was conducted for comparison of sex distribution between groups. Normal distribution of data was checked using the Shapiro-Wilk test. Levene's test for homogeneity of variances was conducted to test the homogeneity between groups. Unpaired t test was conducted for comparison of renin hormone level, Leg musculatures` strength, number and frequency of haemodialysis sessions per month and kidney function test between groups and paired t test was conducted for comparison between pre and post treatment in each group. The level of significance for all statistical tests was set at $p < 0.05$. All statistical analysis was conducted through the statistical package for social studies (SPSS) version 25 for windows (IBM SPSS, Chicago, IL, USA).

**Results:**

**Subject characteristics:**

Table (1) shows the subject characteristics of group A and B. There was no significant difference between groups in age, weight, height, onset and sex distribution ($p > 0.05$).

**Table 1**: Comparison of subject characteristics between group A and B.

| | **Group A** | **Group B** | **p-value** |
|---|---|---|---|
| | **Mean ± SD** | **Mean ± SD** | |
| **Age** (years) | 54.53 ± 2.49 | 53.80 ± 2.02 | 0.082 |
| **Weight** (kg) | 74.12 ± 6.66 | 75.27 ± 4.98 | 0.459 |
| **Height** (cm) | 164.93 ± 4.01 | 166.47 ± 3.43 | 0.168 |
| **BMI** (kg/cm$^2$) | 27.25 ± 2.18 | 27.13 ± 1.48 | 0.797 |

**SD:** standard deviation, **N:** number, **%:** (percentage), **p-value**: Probability value.

**Effect of treatment on renin hormone level leg muscles` strength, and frequency and number of sessions per month:**

**Within group comparison**

There was a significant decrease in renin hormone level and significant increase in leg musculatures` strength post treatment in both groups compared with that pretreatment ($p < 0.001$). The percent of change in renin hormone level and leg musculatures` strength of group A was 66.06%, and 0.8% respectively and that of group B was 67.21% and 16% respectively (Table 2).

There was a significant decrease frequency and number of sessions per month and significant increase kidney function test post treatment in both groups compared with that pretreatment ($p < 0.001$). The percent of change in frequency and number of sessions per month and kidney function test of group A was 1% and 18.55% respectively and that of group B was 3.33% and 19.43% respectively (Table 3).

**Between group comparison**

There was a significant decrease in renin hormone level and significant increase in leg musculatures` strength levels of group B compared with that of group A post treatment (< 0.001), (Table 2).

There was a significant decrease in Frequency and number of sessions per month and kidney function test of group A compared with of group B post treatment (<0.05), (Table 3)

**Table (2):** Mean renin hormone level and leg musculatures` strength pre and post treatment of group A and B.

| | Pre treatment | Post treatment | MD | % of change | p value |
|---|---|---|---|---|---|
| | **Mean ±SD** | **Mean ±SD** | | | |
| **Renin hormone level** | | | | | |
| **Group A** | 41.43 ± 4.18 | 11.11 ± 2.59 | 30.32 | 66.06 | 0.001 |
| **Group B** | 40.86 ± 8.25 | 10.01 ± 1.98 | 30.85 | 67.21 | 0.001 |
| **MD** | 0.57 | 1.1 | | | |
| **t-value** | 0.50 | 1.848 | | | |
| | p 0.621 | **p 0.075** | | | |
| **leg musculatures` strength** | | | | | |
| **Group A** | 2.83 ± 0.46 | 2.87 ± 0.51 | -0.04 | 0.8 | 0.326 |
| **Group B** | 2.53 ± 0.51 | 3.33 ± 0.66 | 0.8 | 16 | 0.001 |
| **MD** | 0.3 | -0.46 | | | |
| **t-value** | 2.523 | -3.50 | | | |
| | p 0.17 | ***p 0.002*** | | | |

**SD:** Standard deviation; **MD:** Mean difference; **p value:** Probability value.

**Table (3):** Mean Frequency and number of sessions per month and kidney function test pre and post treatment of group A and B.

| | Pre treatment | Post treatment | MD | % of change | p value |
|---|---|---|---|---|---|
| | **Mean ±SD** | **Mean ±SD** | | | |
| **Frequency and number of sessions per month** | | | | | |
| **Group A** | 3 ± 0 | 2.96 ± 0.31 | 0.01 | 1 | 0.326 |
| **Group B** | 3 ± 0.30 | 2.99 ± 0.31 | 0.1 | 3.33 | 0.083 |
| **MD** | 0 | 0.07 | | | |
| **p-value** | 0 | 0.326 | | | |
| **Kidney function test** | | | | | |
| **Group A** | 23.3 ± 3.52 | 34.43 ± 3.76 | -11.13 | 18.55 | 0.001 |
| **Group B** | 24.04 ± 4.04 | 35.7 ± 4.07 | -11.66 | 19.43 | 0.001 |
| **MD** | -0.87 | 82.5 | | | |
| **p-value** | 0.342 | 0.001 | | | |

**SD:** Standard deviation; **MD:** Mean difference; **p value:** Probability value.

**Discussion:**

Currently, comprehensive physical therapy could improve physical and functional capabilities, and reduce frequency and dialysis demand thus reduces healthcare costs among individuals with chronic kidney diseases on haemodialysis. Clinical guidelines emphasize the importance of specialized rehabilitation for intradialytic individuals. [3]

Up on that, there is actual need to determine needs of subsequent supervision, level of monitoring required and safety of therapeutic exercise training for individual's chronic kidney diseases on haemodialysis, which will be more efficient in controlling further morbidities, and/ or a higher risk of disability, an increased risk of intradialytic hypotension during haemodialysis, and cardiovascular events as a permanent lifestyle behavior. [21, 22] Therefore, the current study was conducted to investigate the effect of intradialytic neuromuscular electrical stimulation and cycling on renin hormone levels in patients with chronic kidney disease.

The epidemiological point of view in the literature review correlated with what results` of the present study analysis show regarding demographic features of current clinical trial, based on the global CKD published data that had stated that later on aggravate symptoms with various cardiovascular risk factors i.e., sarcopenia. Also, current clinical trial demographic results were in agreement with recognized contributing factor of CKD. [23]

According to current study`s findings, when compared to baseline evaluation, there was a significant improvement in intradialytic cycling exercise protocol group regarding all measured variables (renin hormone level, and leg musculatures` strength, frequency and number od haemodialysis sessions per month, and kidney function tests` values), as there was a significant decrease in renin hormone level and remarkable increase in leg musculatures` strength pretreatment compared with posttreatment with improvements percentage 67.21% and 16%, respectively ($p < 0.05$), there was a significant decrease in frequency and number of sessions per month compared with posttreatment with 3.33% improvement ($p < 0.05$). While regarding group A that showed limited improvements in terms of renin hormone level and leg musculatures` strength, also frequency and number of sessions per month among whom received intradialytic neuromuscular electrical stimulation program.

The results of this study were supported by prior published trial had ensured the sedentary CKD individuals have demonstrated clinical accumulation of protein within tubular lumen thus aggravate renal pathological inflammation and accelerates interstitial fibrosis which patho-physiologically explained based on active renin-angiotensin-aldosterone system.[24] Physiologically, therapeutic physical exercise training strengthens renin- angiotensin-aldosterone system inhibitors have a clinical effectiveness in modulating blood pressure, proteinuria, and delaying CDK progression. [22]

Current study results were correlated with recent study conducted by Heyman et al. [25] who stated that activation of renin-angiotensin-aldosterone system could be induced or accentuated during combined therapeutic exercise protocols in individuals whom suffered of CKD undergoing haemodialysis. Current study results were supported by prior published trial had ensured the Renin angiotensin-aldosterone system inhibitors (RAASis) have demonstrated clinical efficacy in lowering blood pressure, reducing proteinuria, and slowing CKD progression. [26]

In disagreement with current study results, recent clinical trial conducted on whom underlying high renin-angiotensin-aldosterone state not being treated adequately. Where, inadequate hypokalemia might impair renal tubular capabilities to excrete sodium load that raise patients` blood pressure slightly. [27]

Furthermore, advanced clarifying potassium haemodialysis as a crucial in mitigation of hyperkalemia that on the other hand maximizing extent gains of renin-angiotensin-aldosterone. [28]

Fortunately, current study was based on that leg musculatures` strength where exercise requires was feasible and reflected actual daily activities, also it showed desired improvements` indicators for physical functioning i.e., muscular strength and power among CKD patients. Moreover, opposed the idea suggested that VO2 peak was a better predictor of physical improvements, particularly cardiorespiratory fitness over longer follow-up periods rather than strength due to extreme physical deterioration associated with CDK undergoing haemodialysis. [29, 30]

On controversy to current study results, prior clinical trials have reported that exercise capacity is reduced among CKD population, particularly whom in end-stage renal failure. As well, their exercise capacity requires integrated functioning of multiple vital organs. Where, an earlier clinical trial conducted by Sietsema et al. [29] had ensured that individuals within end-stage renal disorders have reduced peak $VO_2$ that reflecting restricted physical exercising capacity. Sietsema and his colleagues had studied 175 ambulatory CDK individuals undergoing haemodialysis, and they had reported that peak $VO_2$ could addressed as a strong predictor for survival status over an extended 3.5 years follow-up. Therefore, could state that exercise testing, and training may represent a useful approach to risk stratification among the most functional population with CKD undergoing haemodialysis.

Current study revealed results were supported with recent published guidelines those enumerated that emphasizing importance in managing CKD undergoing haemodialysis through determining actual kidney functioning parameters in order to identify severity on patho-physiological point of view and detecting incidence of hyperkalemia. [27]

In addition, kidney disease: Improving Global Outcomes (KDIGO) has reported that acceptable guidelines require additional testing and particular medical management in order to control the suspected etiology for CKD. [32]

Where, the intradialytic cycling has been advocated for its effectiveness in improving overall CKD individuals undergoing haemodialysis cardiovascular functioning and their physical capabilities. (33)
Recent clinical trial that disagreed with current study results has recommended overloaded exercise training has been reported as a primary component of a comprehensive rehabilitation based on exercise training program for CKD individuals undergoing haemodialysis. (34)
Overloaded training protocols performed two to three days per week could elicit favorable adaptation and improvement, unless almost followed by post-exercising hypotension that manifested by reduced sympathetic, and parasympathetic activities, plus restricts and deteriorates vascular responsiveness. (35)
Altered autonomic regulation almost reported among CKD undergoing haemodialysis documented based on accelerated sympathetic activation. (36)

**Conclusion:**

Up on current study revealed results both intradialytic neuromuscular electrical stimulation and intradialytic cycling resulted in improve renin hormone level, leg musculatures` strength, and kidney functioning, which reduce frequency and number of haemodialysis among dialysis patients with chronic kidney disease.

**Limitations:**

No follow up was conducted in the current study.

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**Conflict of interest:**

No potential conflict of interest was reported by the authors.

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