# Effects of Predialytic Exercise Training and Detraining on Physical Fitness and Inflammation in Hemodialysis Patients

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## 1. Introduction

Patients receiving maintenance hemodialysis (HD) account for over 0.04% of the global population and contribute to an increasing burden on healthcare systems [1]. Among individuals under maintenance HD, physical fitness deterioration and chronic fatigue are well- documented conditions [2]. Notably, low cardiorespiratory fitness (CRF) and sarcopenia are significant predictors of cardiovascular events and mortality [3, 4], and are also associated with reduced health-related quality of life (QOL) [5]. Patients on maintenance HD are generally sedentary [6]; and exercise therapy has been suggested to improve cardiovascular morbidity and mortality in this population [7].

Regarding the timing of exercise training, two approaches are commonly used: exercise during hemodialysis (HD) and on non-HD days. The protocols of the former primarily consist of supine or seated exercises, such as aerobic cycling or resistance exercises using Thera-bands or weighted ankle cuffs [8]. Exercise training on non-dialysis days offers advantages, including unrestricted upper limb movement, higher-intensity training, and a lower risk of catheter dislodgement, bleeding, and hypotension. However, hospital-based protocols on non-HD days exhibited a higher dropout rate [9].

Only a few studies have investigated hospital-based exercise training prior to hemodialysis (HD). To the best of our knowledge, five such studies have been reported. Of these, four focused exclusively on resistance training (RT) [10-13], while the fifth examined a virtual reality program with diverse exercise modalities [14]. None of the studies investigated a structured program combining cyclic aerobic and resistance training, nor did they conduct any evaluation after a period of time following training discontinuation. Additionally, only one study assessed the effects of training on systemic inflammation [13]. Please refer to the Discussion for details.

Hemodialysis patients often exhibit chronic inflammation, impairing muscle protein synthesis and affecting body composition and function [15]. While exercise may reduce inflammation [16], the effect of pre-dialytic exercise—performed in a hypervolemic state—on systemic inflammation, either positively or negatively, remains unclear.

This study aimed to evaluate the effects of pre-dialytic exercise conducted 1–2 hours before HD (PDE) on muscular and cardiorespiratory fitness, QOL, and inflammatory cytokines. A within-subject design included a 3-month control, 6-month training, and 3-month follow-up. We hypothesized that PDE would improve CRF, quadriceps strength, body composition, QOL and systemic inflammation. Gold-standard measurements of physical fitness including body composition analysis using dual-energy x-ray absorptiometry (DXA), isokinetic dynamometry (isok) and cardiopulmonary exercise test (CPET) were employed. Additionally, a 3-month post-training follow-up assessed carry-over effects.

## 2. Materials and Methods

### 2.1. Study protocol

Participants were eligible for inclusion if they had been undergoing HD for more than 3 months, were over 20 years of age, had adequate dialysis (Kt/V > 1.2), obtained approval from their nephrologist, and were able to walk independently for more than 10 meters. Exclusion criteria included recent hyperkalemia, medical or orthopedic conditions, muscular or psychological disorders, and a history of heart failure or inability to participate in cycling or exercise testing. This study was approved by the Chang Gung Medical Foundation Institutional Review Board. It was conducted between July 2020 and February 2025. All participants provided written informed consent after the researchers explained the experimental procedures. The study complied with the tenets of the Declararetion of Helsinki.

This study employed self-controlled design. Over the study period, each participant underwent assessments at five time points (T1, T2, T3, T4, and T5) with about 3 months between each time point. Between T1 and T2 was the control phase, the participants received usual medical care only. Between T2 and T4 was the training phase, exercise training and nutrition education were implemented. The T4–T5 follow-up phase monitored changes after training cessation with standard medical care only (Fig 1).

The assessment involved CPET, isok, hand grip strength (HGS), DXA, mini-nutritional assessment (MNA), generic and CKD-specific quality of life (Kidney Disease Quality of Life, KDQOL), International Physical Activity Questionnaire (IPAQ), plasma inflammatory cytokine and white blood cell differential counts (Fig 1).

**2.2. Exercise training program**

Before training, an exercise physiologist assessed safety risk profiles and provided an exercise prescription. Then, it was carried out by a properly trained physical therapist. Contraindications for exercise training primarily followed the guidelines of the American College of Sports Medicine. Common conditions included a resting sinus heart rate > 100 bpm and blood pressure > 180/110 mmHg [17]. Blood pressure and ECG were monitored throughout each session. The participants visited the rehabilitation center twice or three times weekly and about 72 sessions in total, which lasted between 24 and 36 weeks. The exercise prescription comprised cyclic aerobic and resistance training. The training was performed 1-2 hours before HD. Cycle ergometry (Lode Corival V3), recumbent stepper (Nustep) and treadmill (Biodex) were used. The intensity was set initially at ventilatory anaerobic threshold (VAT) based on CPET. The duration was 30 minutes per session plus 3-minute warm-up and 3-min cool-down. Once the patient was able to tolerate intensity at VAT for 20 minutes continuously, high-intensity interval training (HIIT) was implemented. The training intensity was given initially at 40% peak work rate (low) for 2 minutes and followed by 80% peak work rate (high) for another 2-min interval. The intensity changed repeatedly at high and low intensity throughout the session. Brief pauses were allowed during a single training session. If the patient could complete a single session without any pause, the high intensity of HIIT was adjusted to increase 5% (for example, 80% to 84%) [18]. Additionally, cyclic RT was performed using isokinetic training system (BodyGreen). Eight devices were applied: leg press, thigh adduction/abduction, leg extension/curl, shoulder press/pull down, pec dec/fly, wait twist, chest press/seated rowing. In each session, three devices were adopted. Ten repetitions were performed with maximal volitional effort in each device.

Please refer to S1 for detailed information on methodology. **2.3**. Nutrition Program; **2.4**. Cardiopulmonary exercise testing; **2.5**. Body composition; **2.6**. Isokinetic dynamometry; **2.7**. Hand grip strength; **2.8**. Hong Kong Chinese Kidney Disease Quality of Life; **2.9** International Physical Activity Questionnaire (IPAQ); **2.10.** Measurement of plasma inflammatory cytokines and white blood cell differential counts.

### 2.11. Statistics

The values were expressed as median (1$^{st}$ quartile, 3$^{rd}$ quartile). Various parameters across five time points (T1 to T5) were analyzed using mixed model of repeated measurements. The overall type 3 fixed effect of staging (T1 to T5) and pairwise comparison were calculated. The significance was set at *p*-value less than 0.05.

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## Supplementary document

### S1. Methodology

### 2.3. Nutrition Program

After T2 assessment, the participants were first required to complete an estimated food record in the past 7 days. A dietitian then conducted a nutritional assessment to provide a comprehensive evaluation and to estimate the required amount and relative proportions of macronutrients. Based on this assessment, food-based dietary advice was given. Each participant received a logbook, and adherence to the dietary recommendations was monitored by the dietitian. For dialysis patients, the recommended energy and protein intake were 25–32 kcal/kg and 1.2–1.3 g/kg of body weight, respectively [39, 40]. After each training session, the participants were provided with a commercially available high-protein supplement (Red Cow Aiji®).

### 2.4. Cardiopulmonary exercise testing

A symptom-limited incremental exercise test was conducted on a calibrated bicycle ergometer (Ergoselect 150P, Germany) to assess aerobic fitness. The test began with an 1-minute warm-up at 10 watts, followed by a 10-watt-per-minute increase until exhaustion, targeting 60 ± 3 revolutions per minute (rpm). Breath-by-breath minute ventilation ($\dot{V}e$), oxygen consumption ($\dot{V}O_2$), and carbonic dioxide production ($\dot{V}CO_2$) were recorded using MasterScreen CPX (Cardinal-health Germany). Heart rate, arterial pressure, and oxygen saturation were monitored using a 12-lead electrocardiogram, an automatic blood pressure system (Tango, SunTech Medical, UK), and a pulse oximeter (Nonin Onyx 9500, USA), respectively. The test ended if the participants fell below 50 rpm, reached volitional fatigue, showed a peak $\dot{V}O_2$ plateau/decline despite continued exercise, or experienced cardiovascular events. Data were averaged every 15 seconds. Ventilatory anaerobic threshold (VAT) was determined using V-slope method and confirmed by non-linearity of $\dot{V}CO_2$ vs. $\dot{V}O_2$, increased $\dot{V}e$-$\dot{V}O_2$ ratio without a rise in $\dot{V}e$-$\dot{V}CO_2$ ratio, and rising end-tidal oxygen without declining end-tidal carbon dioxide [41].

### 2.5. Body composition

This study utilized a fan-beam DXA body composition analyzer (Lunar Prodigy; GE Healthcare, Madison, WI), with data analyzed by GE Encore 12.30 software. The analyzer was calibrated before use, and scans were conducted in standard mode. Results were automatically analyzed and verified by trained professionals. Radiologists ensured participants maintained consistent posture: lying centered on the machine with foam bricks keeping their feet 15 centimeters apart and palms 3 centimeters from the torso. This process measured fat mass, muscle mass and appendicular skeletal muscle mass index (ASMI) [42].

### 2.6. Isokinetic dynamometry

Quadriceps peak torque (PT) was measured using a Biodex isokinetic dynamometer (System 4 Pro™; New York, NY, USA). Isometric PT (IPT) was measured at 45°, and concentric PT across a 90°–0° range. Participants exerted five maximal-effort repetitions at angular velocities of 0°/s, 60°/s, and 120°/s, with a 2-minute rest between sets. Tests with >10% variance were repeated [43]. After a 10-minute rest, participants performed a fatigue test at 120°/s, consisting of 20 maximal-effort concentric contractions. Tests with a variance greater than 15% were repeated [25]. Total work was calculated as the energy exerted during the 20 repetitions, and the fatigue index (%) measured the work decline in the final one third repetitions compared to the initial one third [44].

### 2.7. Hand grip strength

Hand grip strength (HGS) was measured using a dynamometer (Tsutsumi Company , Tokyo). Participants stood with palms facing their bodies, adjusting the grip for optimal force. They squeezed the dynamometer maximally for 3 seconds in two trials per hand, alternating sides. The highest value from each hand was averaged [45].

### 2.8. Hong Kong Chinese Kidney Disease Quality of Life

The KDQOL-SF™ v1.3 survey was used to assess quality of life in patients with chronic kidney disease in HK, tailored for Mandarin speakers with high responsiveness in this population [46]. It includes the 11-item Short Form Health Survey and 17 kidney disease-specific items. The former covers eight categories: physical functioning, role-physical, pain, general health, emotional well-being, role-emotional, social function, and energy/fatigue, summarized into physical component summary (PCS) and mental component summary (MCS) scores. The latter covers 11 domains: symptom/problem list, effects of kidney disease, burden of kidney disease, work status, cognitive function, quality of social interaction, sleep, social support, dialysis staff encouragement, overall health, and patient satisfaction, excluding the sexual function domain [47].

## 2.9 International Physical Activity Questionnaire (IPAQ)

The Taiwan version of the IPAQ [48] was used to evaluate participants' physical activity levels, including vigorous, moderate, walking activities, and sitting, over the past 7 days. Participants reported their engagement in vigorous activities (e.g., running), moderate activities (e.g., light cycling), and walking for commuting or leisure, along with sitting time for desk work or TV. Total physical activity (TPA) was calculated as: (vigorous activity time × 8) + (moderate activity time × 4) + (walking time × 3.3) [49].

## 2.10. Measurement of plasma inflammatory cytokines and white blood cell differential counts

Venous blood collection was performed by medical professionals at the hemodialysis center before hemodialysis (HD). A total of 3 mL of blood was drawn from the arteriovenous shunt of each participant and placed into tubes containing Sodium Heparin 158 USP. Plasma was separated by centrifugation at 1,300 × g for 15 min at 4°C within one hour of collection and then stored at -80°C until analysis. Interleukin (IL)-1 beta (β), IL-6, IL-8, IL-10, IL-12p70, and tumor necrosis factor-α (TNFα) concentrations were detected in plasma using the BD Cytometric Bead Array (CBA) Human Inflammatory Cytokines Kit (Becton-Dickinson) and analyzed with FCAP Array™ software [50].

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