

# Effect of intradialytic aerobic exercise on patients with diabetic nephropathy

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## Background

Diabetes is a major health problem in nowadays' society, as the number of patients with diabetes is growing continuously with their diabetic complications, especially kidney diseases, which is the most feared complication because of its substantial comorbidity, cost, and mortality.

## Purpose

The aim of this study was to determine the effect of intradialytic aerobic exercise on kidney functions tests [serum calcium, serum creatinine, urine creatinine, urine albumin, and estimated glomerular filtration rate (GFR)] in patients with diabetic nephropathy.

## Materials and methods

Thirty patients of both sexes (19 male and 11 female) under hemodialysis with a mean age of 54.13±4.32 years were selected from the renal rehabilitation unit of Edfou General Hospital. They were assigned randomly to two groups of equal number. Group A received a moderate-intensity intradialytic aerobic exercise program (12–13 on rate of perceived exertion scale), and group B received their regular dialysis program only. The treatment program continued for 8 weeks (three exercise sessions per week). Laboratory investigations for serum calcium, serum creatinine, urine creatinine, urine albumin, and estimated GFR were carried out at the beginning and after the end of the treatment program in both groups.

## Results

The results of this study revealed a significant increase in serum calcium in group A compared with group B, and a significant decrease in serum creatinine and urine creatinine in group A compared with group B ( $P=0.03$  and  $0.04$ , respectively). There was no significant change in urine albumin and estimated GFR between the two groups.

## Conclusion

Moderate-intensity intradialytic aerobic exercise (12–13 rate of perceived exertion scale) is beneficial in modulating serum calcium, serum creatinine, and urine creatinine in diabetic nephropathy patients.

## Keywords:

aerobic exercise, chronic kidney disease, diabetic nephropathy, dialysis

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## Introduction

Chronic kidney disease (CKD) is characterized by abnormal kidney function and/or structure. It is common, and often exists together with other conditions (e.g. cardiovascular disease and diabetes) [1]. This global epidemic of diabetes is in large part due to obesity and sedentary lifestyle. The major determinants of kidney disease and its progression to end-stage kidney failure, especially in type 2 diabetes are uncontrolled blood glucose, blood pressure, and albuminuria [2].

Complications of diabetes include macrovascular complications (coronary heart disease, peripheral vascular disease, and cerebrovascular accident) and microvascular complications (neuropathy, retinopathy,

and nephropathy) [3]. Diabetic nephropathy is a progressive kidney disease caused by angiopathy of capillaries in the kidney glomeruli. It is characterized by nephrotic syndrome and diffuse glomerulosclerosis. It is due to longstanding diabetes mellitus, and is a prime indication for dialysis in many developed countries. It is classified as a small blood vessel complication of diabetes [4].

It is established that hemodialysis (HD) patients have low levels of physical activity compared with

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their age-matched controls [5]. Physical inactivity has also been associated with lower levels of self-reported physical functioning (particularly lower extremity), a higher prevalence of cardiovascular disease [6], and an increased level of all-cause and cardiovascular mortality [7].

Exercise plays an important part in diabetes prevention and management [8]. Previous studies found that exercise can reduce hemoglobin A1C levels in patients with type 2 diabetes mellitus and improve cardiovascular fitness, reduce blood pressure, and improve lipid profile [9]. Oxidative stress and inflammation were also improved after exercise [10].

According to the American College of Sports Medicine and American Heart Association, to the reduce risk for cardiovascular events, individuals with chronic illnesses should perform moderate-intensity physical activity for 30 min, five times weekly [11]. In addition, Stack and Murthy [12] reported that physical exercises performed four-to-five times a week reduced the risk for death of physically active patients under HD by about 30%, when compared with sedentary patients; this is in agreement with the recommended features of this study.

As glycemic control, blood pressure control, and oxidative stress are believed to play an integral role in the pathogenesis of diabetic nephropathy, it is logical to hypothesize that exercise has beneficial effects against diabetic nephropathy. However, few studies [13–16] have focused on this topic, and their results were inconclusive.

Being physically active on a regular basis will promote a range of health benefits, including reduced likelihood of cardiovascular disease, diabetes, and some cancers, strengthened heart and cardiovascular system, increased muscle strength, stronger bones, especially if the activity is weight bearing, improved stamina, lowered blood cholesterol levels, reduced blood pressure, and loss of excess body fat [17]. Exercise for renal patients with diabetes is very important, and studies reported that staying active is the best choice to be healthy and being active every day in many ways, such as walking, cycling, and doing things by themselves [18]. Daily physical exercise of moderate-intensity physical activity for 30 min is important for patients with renal dialysis, such as a brisk walk or cycling. The 30 min need not be continuous and can be combined with short sessions of different activities of around 10–15 min each [18].

It is known that inactivity, muscle wasting, and reduced physical functioning, especially for those on long-term dialysis, are associated with increased mortality in CKD. Exercise in patients receiving regular dialysis as a treatment for end-stage renal disease was first introduced 3 decades ago, but is still only offered in a minority of renal units around the world, despite a significant body of evidence to support its use. Work is needed to increase awareness of the potential benefits of increased physical activity for patients with advanced CKD [18].

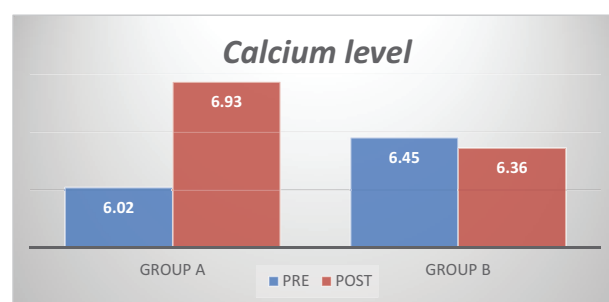
Thus, the aim of this study was to determine the effect of intradialytic aerobic exercise on renal function tests in patients with kidney disease secondary to diabetic nephropathy.

## Materials and methods

### Participants

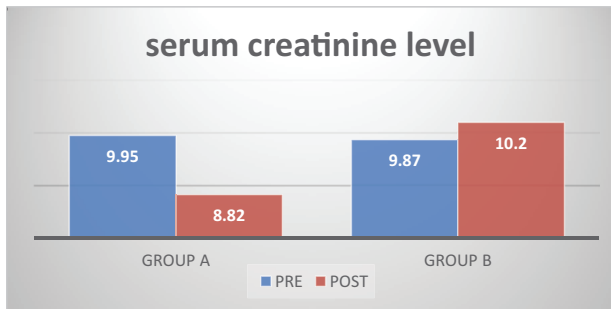
The sample size was estimated as per work of research methods and reporting [19]. Totally, 54 patients were assessed for eligibility to participate in this study ( $n=54$ ) from Edfu General Hospital for being under dialysis as a complication of diabetes and not any other cause (Figs. 1–5). Totally, 16 patients were excluded for not meeting the inclusion criteria ( $n=16$ ), four patients declined to participate ( $n=4$ ), and four patients died during the study ( $n=4$ ). Totally, 30 patients ( $n=30$ ) of both sexes (19 male and 11 female) under renal HD for more than 3 months and with a mean age of  $54.13 \pm 4.32$  years were enrolled in this study. All patients gave their written informed consent for the participation in the study that had been preceded by the explanation of the aim of the study and its course, their role in it with regard to time and money, assurance of protection of the obtained data, and information about free willingness to participate in the study and the possibility to withdraw from the study at any time. This study was approved by the Ethics Committee for

Figure 1



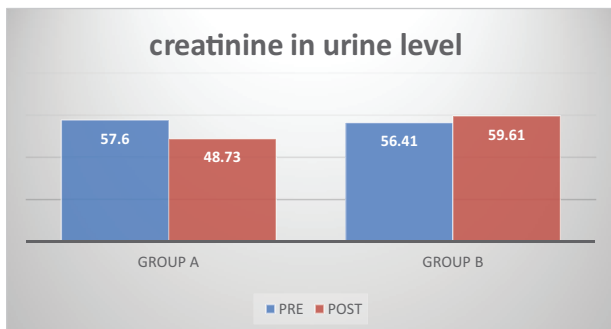
Flow diagram of the progress through the phases of a parallel randomized trial of two groups (i.e. enrollment, intervention allocation, follow-up, and data analysis) [20–22]

Figure 2



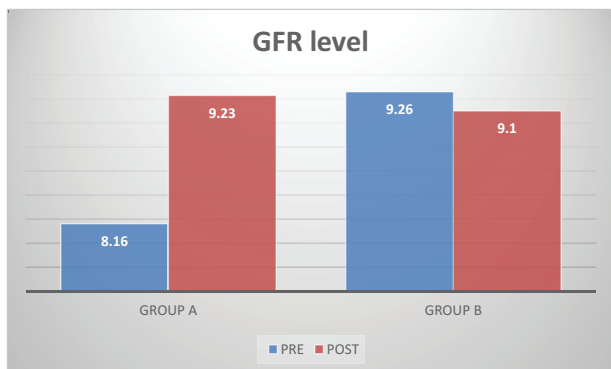
Serum creatinine level

Figure 3



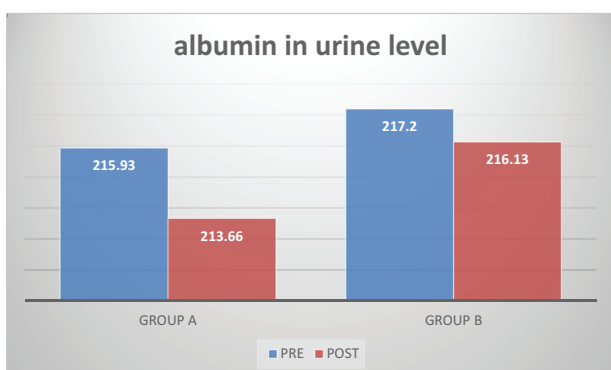
Urine creatinine level

Figure 4



GFR level

Figure 5



Urine albumin level

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Patients were included if they were diagnosed as having type 2 diabetes for more than 10 years. They were diagnosed as having CKD secondary to diabetic nephropathy. It is differentiated from acute kidney disease (acute kidney injury) in that the reduction in kidney function must be present for over 3 months [23]. The patients were on HD for more than 3 months. Their ages ranged between 40 and 60 years. The study included both sexes (male and female) and BMI ranged from 29 to 36. All of the patients had a sedentary lifestyle.

Patients were excluded if they had poorly controlled hypertension, uncompensated heart failure, cardiac arrhythmia requiring treatment, recent unstable angina, persistent hyperkalemia before dialysis, significant valvular heart disease, myocardial infarction within the past 6 months, significant cerebral or peripheral arteriosclerosis, bone disease with a risk for fracture, orthopedic, or musculoskeletal limitations, a recent significant change in the resting echocardiography, third-degree atrioventricular heart block without pacemaker, severe aortic stenosis, suspected or known dissecting aneurysm, active or suspected myocarditis or pericarditis thrombophlebitis or intracardiac thrombi, and recent systemic or pulmonary embolus and acute infection.

#### Evaluation procedures

All patients were initially assessed for their weight and height using weight and height scale to calculate BMI, and assessed for their vital signs as well. Laboratory investigations (kidney functions) were carried out for both groups before and after 8 weeks of aerobic exercise program. Blood and urine samples were taken to measure urine albumin and creatinine levels, serum creatinine level, serum calcium level, and estimated glomerular filtration rate (GFR) using the following formula [24,25]:

$$eC_{Cr} = \frac{(140 - \text{age}) \times \text{mass (kg)} \times (0.85 \text{ if female})}{72 \times \text{serum creatinine (mg/dl)}}$$

#### Treatment program

Patients were randomly assigned (simple randomization) to two groups of equal number, group A and group B. Each group consisted of fifteen patients: group A included 10 male and five female patients, and group B included nine male and six female patients. Group A received treatment

program consisting of intradialytic aerobic exercise for 8 weeks, whereas group B did not receive any exercise program and acted as the control group. Group A received a program of moderate-intensity aerobic exercise [26] [12–13 rate of perceived exertion scale (RPE)] using Bicycle ergometer Zhejiang pedal exerciser, Zhejiang Todo Hardware Manufacture Co. Ltd, Zhejiang China (Mainland), with an exercise period of 30 min. The exercise period comprised the following: the warming up phase (3–5 min), which included aerobic movement exercise of range of motion joints: rotating the wrist (20 rpm clockwise and 20 rpm counter clockwise), wrist up and down (up to 20 moves on the forearm), ankle twisting motion (40 rotations clockwise and counterclockwise around the ankles), and ankles up and down (20 times); the actual phase (20–30 min), which included cycle ergometer exercise with 12–13 RPE; and finally the cooling down phase (3–5 min) in the form of the same aerobic movements as performed in the warming up phase. Because of the study aims and design, the use of  $\text{VO}_2$  max was not an option. In addition, the use of target heart rates in dialysis patients is unreliable as they have abnormal exercise heart rate responses, because of frequently prescribed medications that affect their heart rate response, especially if they are hypertensive (e.g.  $\beta$ -blockers). Furthermore, an individual's heart rate response may be influenced by fluid status. Therefore, the RPE scale was used to detect exercise intensity.

The unwanted events during exercise were controlled by performing the exercise in the first 2 h of the dialysis session to avoid the cardiovascular decompensation and by following the precautions and contraindications to exercise in renal patients. Moreover, we stopped the exercise session and called for medical supervision if unwanted events occurred.

**Table 1 Descriptive statistics and t-test for the mean age, weight, height, BMI, systolic blood pressure, diastolic blood pressure, blood glucose level, and duration of diabetes of both groups (study and control)**

	Group A (mean $\pm$ SD)	Group B (mean $\pm$ SD)	P- value
Age (years)	54.13 $\pm$ 4.32	53.26 $\pm$ 3.17	0.53
Weight (kg)	80.64 $\pm$ 11.12	80.27 $\pm$ 14.25	0.93
Height (cm)	165.6 $\pm$ 7.2	163 $\pm$ 8.22	0.36
BMI (kg/m <sup>2</sup> )	29.46 $\pm$ 4.2	30.31 $\pm$ 5.75	0.64
Systolic blood pressure (mmHg)	150.57 $\pm$ 10.5	149.5 $\pm$ 8.51	0.76
Diastolic blood pressure (mmHg)	100.42 $\pm$ 8.02	99.14 $\pm$ 7.7	0.66
Glucose level	13.13 $\pm$ 1.13	13.07 $\pm$ 1.09	0.88
Duration of diabetes (years)	20.21 $\pm$ 4.85	18.64 $\pm$ 4.87	0.4

MD, mean difference

### Statistical analysis

Descriptive analysis was used for all measured parameters in the form of mean and SD. Level of significance for all tests was set at  $P$ -value of 0.05. Paired and unpaired  $t$ -test was used to compare the results of serum calcium, serum creatinine, urine creatinine urine albumin, and GFR within and between the two groups.

### Results

Independent  $t$ -tests showed no significant differences between the two groups in the age, weight, height, BMI, blood pressure, glucose level, and duration of diabetes (Table 1). In group A, there was a significant increase in Ca and GFR after treatment compared with pretreatment values ( $P=0.0001$  for both), whereas there was no significant difference in Ca or GFR between pretreatment and post-treatment values ( $P=0.42$  and  $0.22$ , respectively) in group B (Tables 2 and 3). In group A, there was a significant decrease in serum creatinine and urine creatinine after treatment compared with that before treatment ( $P=0.0001$  for both) (Table 2). In group B, there was no significant difference in serum creatinine or urine creatinine between pretreatment and post-treatment levels ( $P=0.07$  and  $0.27$ , respectively) (Table 3). There was no significant difference in urine albumin before and after treatment in both groups (group A,  $P=0.1$  and group B,  $P=0.16$ ) (Tables 2 and 3).

A significant difference between the two groups in serum calcium, serum creatinine, and urine creatinine was found. Serum calcium increased significantly by 15.11% in group A compared with group B at the end of the treatment program. Moreover, serum creatinine and urine creatinine decreased significantly by 11.53 and 15.39%, respectively, in group A compared with group B at the end of the treatment program (Tables 4 and 5).

However, there was no significant change in urine albumin between the two groups ( $P=0.85$ ). Although the estimated GFR was increased in group

**Table 2 Paired t-test for comparison between pretreatment and post-treatment mean values of group A**

Parameters	Pretreatment (mean $\pm$ SD)	Post- treatment (mean $\pm$ SD)	MD	P- value
Ca (mg/dl)	6.02 $\pm$ 0.54	6.93 $\pm$ 0.69	-0.91	0.0001
Serum creatinine (mg/dl)	9.95 $\pm$ 1.02	8.82 $\pm$ 1.05	1.13	0.0001
Urine creatinine (mg/kg/24 h)	57.6 $\pm$ 9.97	48.73 $\pm$ 8.85	8.87	0.0001
Urine albumin (mg/l)	215 $\pm$ 41.15	213.66 $\pm$ 40.69	2.27	0.1
GFR	8.16 $\pm$ 1.97	9.23 $\pm$ 2.13	-1.07	0.0001

GFR, glomerular filtration rate; MD, mean difference.

A, compared with group B, there was no significant difference ( $P=0.87$ ) between the two groups (Tables 4 and 5).

## Discussion

In the present study, the results revealed a significant increase in serum calcium in group A compared with group B. Furthermore, there were significant decreases in serum creatinine and urine creatinine in group A compared with group B in response to the designed exercise program. However, there was no significant change in urine albumin between the two groups. Although the estimated GFR was increased in group A compared with group B, there was no significant difference between the two groups.

The results of this study are in agreement with a study by Yu *et al.* [27], who studied the effect of physical

**Table 3 Paired t-test for comparison between pretreatment and post-treatment mean values of group B**

Parameters	Pretreatment (mean±SD)	Post-treatment (mean±SD)	MD	P-value
Ca (mg/dl)	6.45±0.88	6.36±0.77	0.09	0.42
Serum creatinine (mg/dl)	9.87±2.02	10.2±2.1	0.33	0.07
Urine creatinine (mg/kg/24 h)	56.41±10.24	59.61±18.12	-3.2	0.27
Urine albumin (mg/l)	217.2±34.61	216.13±33.38	1.07	0.16
GFR	9.26±2.29	9.1±2.47	0.16	0.22

GFR, glomerular filtration rate; MD, mean difference.

**Table 4 t-Test for comparison of pretreatment mean values between the two groups**

Parameters	Group A (mean±SD)	Group B (mean±SD)	P-value
Ca (mg/dl)	6.02±0.54	6.45±0.88	0.11
Serum creatinine (mg/dl)	9.95±1.02	9.87±2.02	0.88
Urine creatinine (mg/kg/24 h)	57.6±9.97	56.41±34.61	0.75
Urine albumin (mg/l)	215.93±41.15	217.2±34.61	0.92
GFR	8.16±1.97	9.26±2.29	0.17

GFR, glomerular filtration rate; MD, mean difference.

**Table 5 t-Test for comparison between post-treatment mean values of both groups (group A and group B)**

Parameters	Group A (mean±SD)	Group B (mean±SD)	MD	P-value
Ca (mg/dl)	6.93±0.69	6.36±0.77	0.57	0.04
Serum creatinine (mg/dl)	8.82±1.05	10.2±2.1	-1.38	0.03
Urine creatinine (mg/kg/24 h)	48.37±8.85	59.61±18.12	-10.88	0.04
Urine albumin (mg/l)	213.66 ±40.69	216.13 ±33.38	-2.47	0.85
GFR	9.23±2.13	9.1±2.47	0.13	0.87

GFR, glomerular filtration rate; MD, mean difference.

activity on diabetic nephropathy in particular in a long study continued for more than 1 year, in that they could not identify physical activity as an important factor for reducing albuminuria and estimated GFR.

Although the effect of physical activity on diabetic nephropathy remains controversial, patients with diabetic nephropathy are at a high risk of developing cardiovascular disease [28]. Physical activity improves the glycemic index, blood pressure, and lipid control [29]. These are all important cardiovascular risk factors. Physical activity can improve patient's quality of life as well [30]. Thus, increased physical activity should be encouraged among patients with diabetes mellitus.

Moreover, Kurdak *et al.* [31] reported that, after 8 weeks of aerobic exercise in streptozotocin-induced diabetic rats, there was no significant difference in albumin in urine level between the study and the control group, whereas GFR value was lower in the exercise group, which coincides with our study result. This is contradictory to our study results but these rats were only diabetic and did not have a renal failure.

In addition to these results, the results of Yuji *et al.* [32] were in line with this study in that, after 8 weeks of exercise on mice with diabetic nephropathy, there was no significant difference in urine albumin level or GFR value between the study and the control group (despite a slight increase in GFR in the study group and a slight decrease in urine albumin level, but not statistically significant).

The result of this study coincides with the results of a study by El-Nahas *et al.* [33], who studied the effects of different exercise intensities on serum electrolyte level in HD patients. The study showed that moderate-intensity aerobic exercise increases serum calcium level (improvement of 12.29%) and seems to induce positive calcium balance more than light-intensity exercise (improvement of 4.23%). This point was approved by Zaher *et al.* as well [34].

The results of the present study as regards serum calcium level coincide with the data presented by Vaithilingham *et al.* [35], who suggested that an aerobic exercise regimen for 15 min during HD sessions improves serum calcium levels in a period of 8 weeks. This observation might be attributed to the direct beneficial effects of aerobic exercise or general effects of regular intradialytic exercise.

Although many studies agree with the results of the present study, Makhloogh *et al.* [36] reported that

15 min of intradialytic aerobic exercise could not induce a significant difference in serum calcium level. This is contradictory to our study results. In this study, they investigated the effect of low-intensity (not moderate-intensity) intradialytic aerobic exercise on serum electrolyte level in HD patients, which may be a factor explaining this contradiction. Azra *et al.* [37] agreed with this and reported that there was no significant difference in serum electrolytes between active and passive pedaling intradialytic exercise. This result differs from present study results; this may be due to the small sample size in the study by Azra (16 participants only).

The present study is in agreement with the study by Afshar *et al.* [38], who compared between the effects of aerobic and resistance training in patients on maintenance HD. They reported that there was a significant reduction in serum creatinine for the aerobic type of exercise. However, there was no effect on serum albumin and body weight.

Parsons *et al.* [39] reported that combined program of aerobic and resistance training using cycle ergometer thrice weekly for 45 min (3–5 min bouts) did not induce a significant difference in serum creatinine, and the only significant changes observed were the increase in dialysate urea removal. This discrepancy may be due to the small sample size of the study by Parson.

Some results of the present study warrant further investigations. In addition to the need to study the effect of exercise on some other parameters (e.g. urea, glucose levels, quality of life, and psychological status) in patients with diabetic nephropathy, the most important is to conduct the research with a large sample size and a study duration of more than 6 months, which is needed to eliminate large discrepancies between different study results. To achieve this large number of samples, multiple researchers in multiple rental units should work together on the same topic.

The high dropout rate of end-stage renal disease was the main limitation that we faced in this study. In addition to this, lack of motivation, psychological status, and connecting needles were other limitations.

## Conclusion

Intradialytic aerobic exercise with moderate intensity showed a significant increase in serum calcium and a significant decrease in serum creatinine and creatinine

in urine in group A compared with group B, which was beneficial in modulating renal function tests for patients with diabetic nephropathy who received the exercise program.

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## Conflicts of interests

There are no conflicts of interest.

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