Original Article

Effect of physical activity and vitamin D compared with vitamin D alone on muscle strength, back flexibility and aerobic activity in patients with chronic kidney disease: A comparative study from Pakistan

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Background and Objectives: To compare the differences in musculoskeletal health with vitamin D alone in comparison with vitamin D with physical activity (PA) among chronic kidney disease (CKD) patients. **Methods and Study Design:** An open labeled, randomized, controlled trial was conducted at two tertiary care centers in Pakistan. Patients with CKD stage 2–4 and vitamin D deficiency (<20 ng/mL) were recruited in the trial. Both the arms were given oral vitamin D (cholecalciferol) drops (4000 IU) once daily for three months. One arm received only vitamin D (VD arm), while the second arm received vitamin D along with PA (VDPA arm). **Results:** Of the 1,235 CKD stage 2-4 subjects contacted, forty-six subjects were enrolled. Eighteen were assigned to VD arm and twenty-eight were assigned to VDPA arm. Between groups comparison shows that bicep strength increases from 15 to 17 kg. Likewise, back flexibility and aerobic fitness also increased among those who receive vitamin D and physical activity, however these differences were not statistically significant (p>0.05). Sensitivity analysis within group comparison shows rise of bicep strength from 13.8 kg to 15.2 kg in the VD alone arm (p=0.05); however, in the VDPA arm, there is a greater difference of 14.3 kg to 17.2 kg (p<0.001). **Conclusions:** Targeted PA among CKD patients has potential to improve bicep strength and back flexibility. However, as the sample size was small, further studies would be required to suggest whether a PA should be included as part of the treatment regimen.

Key Words: Vitamin D, Physical activity, chronic kidney disease, Pakistan

INTRODUCTION

Chronic kidney disease - mineral and bone disorder (CKD-MBD) is a systemic disorder that affects bone, heart and kidney in Chronic Kidney Disease (CKD) patients.[1] It is a major complication of CKD, manifested by abnormalities of biochemical markers of bone metabolism including calcium, phosphorus, parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), and vitamin D.[2,3] In addition, there are abnormalities in bone turnover, mineralization, linear growth, or strength and presence of extra skeletal calcification. Many laboratory targets and therapeutic approaches have been recommended in different clinical practice guidelines since the introduction of the term CKD-MBD in 2006 by Kidney Disease: Improving Global Outcomes (KDIGO).[4,5]

Control of CKD-MBD is crucial in improving the prognosis and quality of life in CKD patients. Loss of skeletal muscle mass and strength due to abnormalities in vitamin D metabolism, other nutritional deficiencies and acidosis have been associated with increased risk of fractures and poor quality of life.[6]

Current evidence suggests a benefit of exercise in im-

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proving physical functioning, reducing skeletal muscle loss and improving cardiovascular implications of CKD.[3] Although several studies have investigated how exercise affects individuals with CKD and the safe and beneficial effects of exercise over the past three decades, few evidence-based guidelines exist; and none of those study the effects on CKD patients in the Pakistani population.

Approximately 15 to 20 percent of Pakistani population over 40 years of age have a reduced estimated glomerular filtration rate (eGFR).[7] Also, 80-90% subjects in general population are vitamin D deficient.[8] CKD, with vitamin D deficiency and sedentary lifestyle further effects musculoskeletal health.[2] KDOQI guidelines recommend vitamin D replacement, however, need and amount of exercise required by CKD patients has not been mentioned. Effect of physical activity alone and physical activity with vitamin D therapy has not been studied in this region.[9] Therefore, we aimed to compare the differences in musculoskeletal health with vitamin D alone in comparison with vitamin D with physical activity of individuals with CKD in the Pakistani population.

METHODS

Study design, setting and subjects

An open labeled, randomized, controlled trial was conducted at Aga Khan University Hospital (AKUH) and The Kidney Centre Post Graduate Training Institute (TKCPGTI) in Karachi, Pakistan, from November 2013 to October 2014. Subjects attending ambulatory nephrology clinics were included according to the following criteria: permanent resident of Karachi, between 20–60 years of age, vitamin D deficiency (<20 ng/mL) with CKD stage 2–4 and an eGFR of less than 60 mL/min; were invited to participate in the study. The CKD stages were defined according to NKF/DOQI guidelines. We excluded transplant recipients, CKD stage 5 or end-stage renal disease (ESRD) receiving dialysis, subjects on vitamin D treatment, history of known vitamin D deficiency-related bone disease, corticosteroids treatment, any known chronic inflammatory disease and malignancy, physical disability leading to inability to perform physical activity, and subjects with known depression. The protocol and consent documents were approved by independent ethics committees at both centers (1624-Med-ERC-10). All patients provided written informed consent. The trial was registered with the Chinese Clinical Trials Registry (ChiCTR2100045116). Figure 1 shows the flow diagram of the participants selection and recruitment at the 2 centers.

Subjects screening, recruitment and randomization

Patients with serum creatinine of ≥1.7 mg/dL for men and ≥1.4 mg/dL for women were identified at the nephrology clinic and their glomerular filtration rate (GFR) were calculated through Cockcroft and Gault equation. Patients with eGFR <60 mL/min were selected and were further assessed for vitamin D deficiency. A cut-off of <20 ng/mL was taken to define Vitamin D deficiency.

Randomization was performed via computer generated random numbers by a statistician. A block randomization strategy was used to periodically balance the assignment in the 2 study arms. Once a patient consented to participate in the study, the research officer obtained treatment assignment by opening the sealed envelope.

Intervention

Both the arms were given oral vitamin D (cholecalciferol) drops (4000 IU) once daily for three months. One arm received only vitamin D (VD arm), while the second arm received vitamin D along with physical activity (VDPA arm). Targeted physical activity included isometric and isotonic exercises for quadriceps and hamstring muscles, stretching exercises for lower back, hamstring and neck muscles, aerobic exercises for lower and upper extremities. MicroFit Fitness Assessment System (FAS-2 System) was used to measure body weight, arm strength, and back flexibility. Bicep strength, back flexibility and fat composition from abdomen and quadriceps, respectively, were also measured. The FAS-2 System is a computerized assessment system of different fitness components. Individual performance can be recorded and compared with previous attempts. It provides for an objective analysis of performance.10 On the basis of FAS-2 System assessment, all the patients in the VDPA arm were prescribed complete home exercise program.

Blood samples for evaluation of serum creatinine, urea, hemoglobin (Hb), albumin, calcium, alkaline phosphatase, and parathyroid hormone (PTH) were collected from study subjects before and after the intervention.

Monitoring

Regular reminders via Short Message Service (SMS) were delivered to the participants by research officers to improve compliance. Compliance was also determined at each monthly visit by research officer by analyzing the empty bottles of vitamin D. Along with this, physical activity was assessed by a physiotherapist at bi-monthly intervals.

Study end point

Our study endpoint was improvement in musculoskeletal health assessed by measuring biceps strength, back flexibility and aerobic fitness.

Statistical analysis

We aimed to detect a 20 percent difference among groups with a power of 80 percent. The rate of symptom relief in the standard group was assumed to be 30 percent. After incorporating 10% of non-response/ attrition, sample size came out to be 120 (60 patients in each group).

Statistical analysis was by group assignment (i.e., intention to-treat), and by level of physical activity. For this analysis, serum 25 hydroxy(OH)D values, biceps strengths, back flexibility and aerobic fitness levels were obtained at baseline and at 3 months to characterize the status of the cohort and its response to treatment. Student's t-tests and paired wise t-tests were used for the between and within group comparison. p values of ≤0.05 were considered significant.

RESULTS

1,235 CKD stage 2-4 subjects were contacted, out of these forty-six subjects were finally enrolled and were randomly assigned to the trial: Eighteen were assigned to

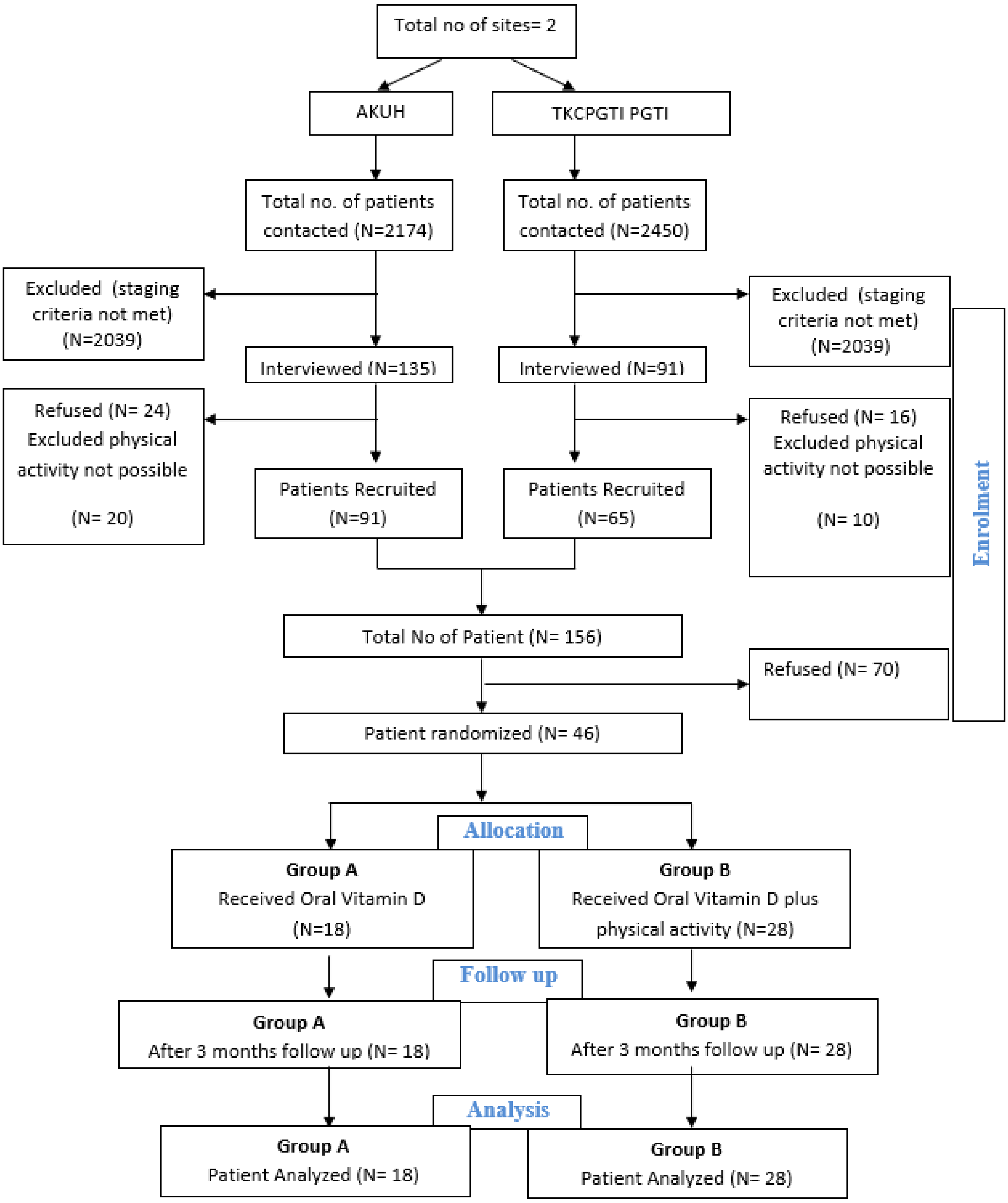

Figure 1. Consort diagram to show process and number of patients enrolled and finally analyzed in clinical trial.

VD arm and twenty-eight were assigned to VDPA arm. Demographic characteristics, biochemical parameters and vitamin D levels were almost comparable between the groups at the baseline (Table 1). The majority of the participants were in the fifth decade of their life, female and vitamin D levels less than 10 ng/mL. Initial strength was 13.8 kg in the VD arm and 14.3 kg in the VDPA arm. Likewise, flexibility was slighter higher in the second arm; however, these differences were statistically insignificant.

Between groups comparison shows that bicep strength increases from 15 to 17 kg (Table 2). Likewise, back flexibility and aerobic fitness also increased among those who receive vitamin D and physical activity, however these differences were not statistically significant (p>0.05).

We also performed a sensitivity analysis by doing within group comparison (Table 3). The bicep strength rises from 13.8 kg to 15.2 kg in the VD alone arm (p=0.05); however, in the VDPA arm, there is a greater difference of 14.3 kg to 17.2 kg (p<0.001). In assessing back flexibility, it increases from 26 cm to 28.5 cm (p=0.61) in the VD arm, however, a significant rise in the VDPA arm (29 cm to 34 cm, p=0.05) was recorded. Aerobic fitness capacity displayed a reduction from 10.5 minutes (min) to 9.5 min in the VD arm (p=0.15) and an increase in the VDPA arm from 12.2 min to 15.8 min (p=0.32).

DISCUSSION

In our study, we tested vitamin D alone and with different levels of physical activity, for first time, in Pakistani population. The targeted physical activity intervention tested

Table 1. Baseline demographic and biochemical characteristics of study participants

Variable	Vitamin D alone (SD) n=18	Vitamin D plus physical activity (SD) n=28
Age (years)	54.6 (±13.8)	46.2 (±13.7)
Gender		
Male	5 (28%)	9 (32%)
Female	13 (72%)	19 (68%)
BMI kg/ m^2	28.8 (±13.1)	25.4 (±4.0)
Bicep strength (kg; mean±SD)	13.8 (±10.3)	14.4 (±6.7)
Back flexibility (cm; mean±SD)	26.3 (±13.1)	29.4 (±12.9)
Aerobic fitness capacity (min; mean±SD)	10.5 (±11.1)	12.3 (±8.9)
Biochemical details		
Vitamin D ng/mL	8.87 (±4.98)	6.47 (±5.25)
Urea mmol/L	61.6 (±26.2)	86.4 (±65.8)
Creatinine mg/dL	1.90 (±0.98)	2.92 (±3.18)
Calcium mg/dL	8.56 (±1.41)	8.48 (±2.51)
Alkaline PO4 U/L	104 (±58.5)	91.9 (±37.6)
Albumin gm/dL	4.41 (±0.69)	4.35 (±0.90)
PTH pg/mL	157 (±151.0)	142 (±123.6)

Table 2. Difference of musculoskeletal health between groups after study

Variable	Vitamin D alone	Vitamin D plus physical activity	*p* value
Biceps strength (kg; mean±SD)	15.2 (±7.1)	17.6 (±7.2)	0.5
Back flexibility (cm; mean±SD)	31.1 (±15.4)	34.6 (±14.4)	0.2
Aerobic fitness capacity (min; mean±SD)	9.5 (±9.6)	15.9 (±10.9)	0.2

Table 3. Difference of musculoskeletal health within groups shown before and after study

Variable	Vitamin D	*p* value	Vitamin D plus physical activity	*p* value
Initial bicep strength (kg; mean±SD)	13.9±10.3	0.05	14.4±6.8	<0.001
Final bicep strength (kg; mean±SD)	15.2±7.1		17.6±7.2	
Initial back flexibility (cm; mean±SD)	26.3±13.1	0.61	29.4±12.9	0.05
Final back flexibility (cm; mean±SD)	31.1±15.4		34.7±14.4	
Initial aerobic fitness capacity (min; mean±SD)	10.5±11.1	0.15	12.3±8.9	0.32
Final aerobic fitness capacity (min; mean±SD)	9.5±9.6		15.9 ±10.9	

in this study showed that the bicep strength and back flexibility improves significantly in patients with CKD treated with physical training and vitamin D as compared to vitamin D alone. However, there was less profound effect on aerobic activity.

A large body of evidence strongly suggests a beneficial effect of physical activity on blood pressure, oxidative stress, vasoactive peptides, attenuation of decease in eGFR, overall improvement in quality of life, and a decrease in mortality.[11-14] Wallin et al., reported that the level of physical activity at baseline was a predictor of 5-year exercise capacity in mild to moderate CKD patients.[15]

There are certain limitations to performing physical activity for CKD patients and an understanding of these factors is important for the management of such patients. CKD or ESRD may lead to exercise intolerance through a variety of central and peripheral factors.[16] Central factors include pulmonary limitations, cardiac limitations, anemia and iron deficiencies, elevated sympathetic nerve activity and abnormal neurocirculatory control, and renal and vascular dysfunction.[17-23] Peripheral contributors to exercise intolerance in CKD patients include skeletal muscle abnormalities and sarcopenia.[24,25]

While our study did not achieve the desired sample size and was not powered to detect differences in musculoskeletal health, we did note changes that could be clinically significant. It is possible that the noted changes in physical activity and overall musculoskeletal health may translate into a better risk factor profile for CKD, as well as improved morbidity and overall quality of life.

To our knowledge, this is the first prospective, randomized trial of exercise training in patients with CKD, along with vitamin D, from Pakistan; so direct comparison with a similar population is not possible. Corrêa et al demonstrated that low-load resistance training with blood flow restriction was effective in preventing renal function decline (eGFR).[13] Kharbteng et al demonstrated an improvement in quality of life of CKD patients with a breathing training program.[12] Zhang et al., reported a decrease in mortality with leisure time physical activity in CKD patients. They reported that physical activity as much as >900 minutes/week was beneficial and resulted in decreased mortality in CKD patients.[11] A thourough review of literature was performed to find similar studies from other countries as well. The characteristics and findings of the most relevant studies are listed in Table 4.

In our study, we recorded physical activity as bicep strength, back flexibility and aerobic fitness. An increase in bicep strength and back flexibility was noted with vitamin D administration even without physical activity. But the vitamin D plus physical activity arm reported significantly larger increases in both bicep strength and physical activity. This supports the evidence that combination of

Table 4. Literature review and characteristics of exercise intervention studies in chronic kidney disease patients

Study	Country	Type of study	N	Age (years)	Control Group	Exercise/ Intervention	Time observed	Priary Outcome	Result
Kharbteng. 2020[12]	India	RCT	60	51.83±10.27	30	BE	4 weeks	QOL	Improve
Pike. 2020[14]	Japan	RCT	111	57	44	AE	4 months	Weekly physical activity	No difference
Zhou. 2020[26]	Sweden	RCT	112	67±13	None	BT or ST + ET	12 months	Progression of AAC	No difference
Hellberg. 2019[27]	Sweden	RCT	151	66±14	None	BT or ST	12 months	Physical performance	No difference
Aoike. 2018[28]	Brazil	RCT	40	55.8±8.3	15	AE	24 weeks	CC, QOL, QOS	Improve
Leehey. 2009[29]	USA	RCT	11	66	4	AE	24 weeks	Proteinuria	Improve
Hiraki. 2017[30]	Japan	RPS	36	68.7±6.8	18	AE + RE	12 months	RF, Handgrip, KEMS	Improved handgrip, KEMS. No change in RF
Leehey. 2016[31]	USA	RCT	36	49-81	18	AE + RE	12 months	UPCR	No difference
Pechter. 2003[32]	Estonia	-	26	31-72	9	AE(W)	12 weeks	LPO and SG	Decreased
Viana. 2014[33]	Englang	-	15	59±10	3	AE	6 months	IL-6:IL-10, T-lymphocyte	Decreased
Nylen. 2015[34]	USA	-	128	62±2.1	None	AE + RE	12 weeks	RF	Improve
Hamada. 2016[35]	Japan	-	47	68.8±11.1	None	AE + RE	6 months	IPAQ	Improve
Kirkman. 2019[36]	USA	RCT	36	58±2	17	AE	12 weeks	Microvascular function	Improve
Barcellos. 2018[37]	Brazil	RCT	150	65	74	AE + RE	16 weeks	eGFR	No change

RCT: randomized controlled trial; BE: breathing exercises; QOL: quality of life; AE: aerobic exercises; BT: balance training; ST: strength training; ET: endurance training; CC: clinical condition; QOS: quality of sleep; RE: resistance exercises; RF: renal function; KEMS: knee extension muscle strength; RPS: randomized pilot study; UPCR: urine protein to creatinine ratio; (W): under water; LPO: lipid peroxidation; SG: serum glutathione; IPAQ: International Physical Activity Questionnaire; eGFR: estimated glomerular filtration rate.

vitamin D supplementation and physical activity helps in improvement of muscle strength and overall fitness of CKD patients.

There are several limitations to this study. It was performed as a pilot project that included only a small number of patients as we cannot achieve our desired sample size in the pre-calculated timelines. We calculated that it would have taken a minimum of 8 more months to achieve the target sample size; we stopped the study due to slow recruitment process and limited funds. Ideally, this trial should be designed to have three arms, with two independent groups receiving only vitamin D or physical activity training; hence independent effect of vitamin D cannot be traced. The combined intervention showed better overall efficacy than vitamin D alone, however we do not know whether the effects of the combined intervention were equally attributable to all the modules. Furthermore, this was a 3- month follow up trial; a longer-term randomized clinical trial would contribute substantially to understanding the long-term effects of vitamin D supplementation and physical activity intervention on outcomes. Moreover, although we gave special attention to improve the compliance by regular reinforcement, non-compliance to physical activity at home cannot be completely ruled out.

This study generates certain directions for the future research in the area of improvement of musculoskeletal health of CKD patients. We suggest integration of comprehensive therapy with medication, along with optimal level of physical activity in early stages of CKD. It should be recommended as standard of care in these patients. This pilot study should serve as incentive to complete a larger randomized trials in the region, examining the impact of exercise on musculoskeletal health and quality of life of CKD patients.

Conclusion

In conclusion, our study suggests that targeted physical activity among CKD patients has potential to improve bicep strength and back flexibility, and should be included as part of the treatment regimen for improved outcomes.

AUTHOR DISCLOSURES

No competing interests are reported.

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