

Original Article

Efficacy and safety of whole body vibration in maintenance hemodialysis patients - A pilot study

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Objectives: The aim of this study was to assess safety and effectiveness of Whole Body Vibration exercise (WBV) to improve physical performance and parameters of inflammation in patients on maintenance hemodialysis (MHD). **Methods:** Prospective, open-label trial in n=14 patients on maintenance hemodialysis. Participants performed WBV twice weekly for 12 weeks before (n=8) or after (n=6) hemodialysis sessions. The primary endpoint was physical performance assessed by the Short-Physical-Performance-Battery (SPPB). Secondary endpoints included established parameters of musculoskeletal assessment and blood chemistry. **Results:** As compared to baseline, physical performance (SPPB) improved significantly (p=0.035). Moderate advances were also seen for 6-Minute-Walking test, Timed-up-and-go test, jumping height and handgrip strength. Improvements were particularly pronounced in subjects with seriously impaired baseline performance. Skeletal muscle index showed a tendency to better values. Laboratory data exhibited a significant reduction of white blood cell count and a trend to lower levels of hsCRP. WBV was generally well tolerated. Two events of clinically significant blood pressure decline occurred in patients exercising after dialysis sessions. **Conclusions:** Results of this pilot study suggest effectiveness and safety of WBV in hemodialysis patients. Beneficial effects may affect both, parameters of physical performance and systemic inflammatory activity, which should be verified in larger scale clinical trials.

Keywords: Maintenance Hemodialysis, Sarcopenia, Exercise, Whole Body Vibration**Introduction**

In end stage renal disease (ESRD), muscle wasting and dysfunction are frequent complications, predisposing to poor quality of life, impaired mobility, frailty and falls, as well as decreased bone mineral density and osteoporosis, altogether being associated with premature death^{1,2}. Uremic myopathy typically affects proximal muscles of the lower extremities and typically leads to type 2 fiber atrophy³. Additionally, intramuscular adipose tissue infiltration, increased muscle

fibrosis and decreased cross-bridge formation as well as neural deficiencies have been described⁴. The multifactorial causes of muscle dysfunction in end stage renal disease include uremic toxins, decreased nutritional status, elevated pro-inflammatory cytokines, oxidative/carbonyl stress, hormonal factors (elevated angiotensin II and glucocorticoid levels, testosterone deficiency among male subjects) as well as poor vitamin D status and insulin resistance along with low levels of insulin-like growth factor¹. This is further accentuated by prevailing co-morbidities, e.g. coronary, cerebral and peripheral artery disease, metabolic acidosis and depression. Above all, sedentary lifestyle especially on dialysis days is a crucial issue in ESRD^{1,5,6}.

Intra-dialytic training was shown to improve physical fitness, cardiovascular functions, physical performance, inflammation and quality of life in ESRD patients. Still, many patients are unable or unwilling to perform such active exercise programs. Pivotal barriers are fatigue, lack of time, and an abundance of medical problems⁷.

Whole-Body-Vibration (WBV) exercise is an effective method for physical training requiring limited effort. Vibration

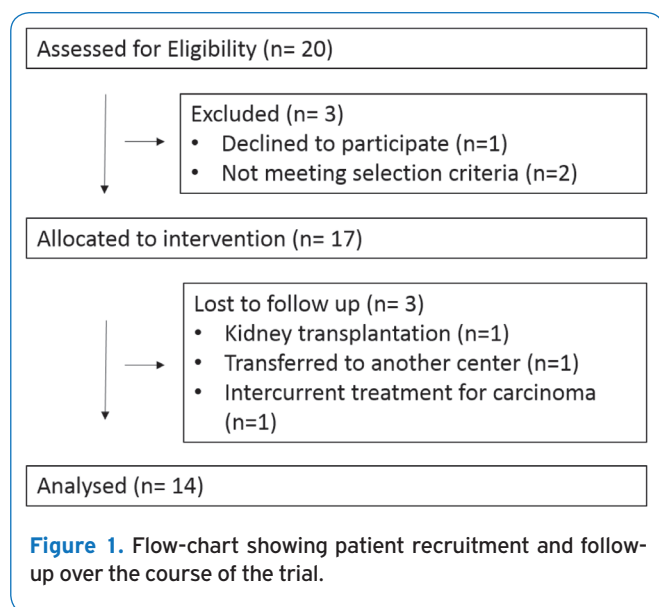
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exercise can be applied with varying intensity, basically characterized by duration, frequency and extent of vibration, i.e. displacement from the lowest to the highest point or the maximum displacement from equilibrium (amplitude)⁸. WBV enhances muscle activity, force, power, balancing ability and flexibility⁹. Furthermore, it may have beneficial effects on prevention and treatment of osteoporosis in terms of improving bone mineral density¹⁰. WBV improves peripheral circulation^{11,12} and reduces arterial stiffness while blood pressure and heart rate do not change from the baseline in most of the studies^{13,14}.

WBV is extensively studied as a means to prevent microgravity and immobility associated muscle wasting and bone loss in space flight and it is getting increasingly popular even among athletes, who combine WBV with conventional exercise^{15,16}. WBV was successfully implemented in prevention of muscle and bone loss after long-term bed rest¹⁷. In elderly subjects, vibration exercise enhanced motor capacity, improved balance and decreased risk of falls¹⁸. Positive results were also reported in Parkinson's disease¹⁹ and stroke patients²⁰.

By now, safety and efficacy of WBV has not been investigated in patients with ESRD. Therefore, we performed this exploratory study in hemodialysis patients in order to elucidate potential effects of whole body vibration exercise on physical performance and various biochemical markers in this condition.

Materials and methods

Design

The study was performed as a prospective, open-label, non-randomized single-center exploratory investigation. The protocol was approved by the competent Ethics Committee

Table 1. Baseline characteristics of the participants.

Participant's Characteristics		
	Mean ± SD	Range
Age (year)	59 ± 11	45-75
Sex (m/f)	8/6	-
Height (cm)	173 ± 8	157-184
Body weight (kg)	73.6 ± 12.6	56-97
Body Mass Index (kg/m ²)	24.5 ± 3.6	19-29
MHD duration (month)	48 ± 61	6-219

at the Medical Faculty of the University of Würzburg (No. 299/13, Chair: Prof. Stolberg) following their consultations on Dec 17th, 2013.

Participants

Written informed consent was obtained from all participants following thorough information about the course and purpose of the study. A total of 20 maintenance hemodialysis patients were recruited from the KfH Kidney Center in Würzburg. Inclusion criteria were adult age (≥ 18 years) and hemodialysis treatment over at least 6 months before enrollment. Exclusion criteria were mainly defined by contraindications against WBV exercise, including recent fractures or surgery (<3 months), non-healed wounds and scars, endoprosthetic implants in trained body regions (knee, hip, ankle replacement), acute joint inflammation, thrombosis within 3 months before enrollment, stone diseases (urinary tract and gall duct), symptomatic discopathy, epilepsy, signs of current infection, pregnancy and open hernias.

Out of 20 patients enrolled, 3 patients could not be included and 3 did not complete the study for different reasons, not related to WBV, such as kidney transplantation, transfer to another hemodialysis center and a new diagnosis of a colon carcinoma. Owing to short-dated occurrence of these events, we were not able to conduct a final assessment in these participants (Figure 1).

Data for final analysis were available for 14 participants (8 males and 6 females) with a mean age of 57.8 (range 45-75) years. Baseline characteristics are outlined in Table 1. The underlying causes for ESRD were glomerulonephritis (n=5), polycystic kidney disease (n=3), nephrosclerosis (n=3), reflux nephropathy (n=2) and diabetic nephropathy (n=1). A total of 7 patients had received kidney transplantation in the past, one of these had a combined kidney and pancreas transplantation. Time on dialysis was 4 years on average, ranging from 0.5 to 18 years. Hypertension was present in all subjects and treated to normal BP values. 12 patients had secondary hyperparathyroidism, two other patients underwent parathyroidectomy and autotransplantation of one parathyroid gland. Cardiovascular disease (coronary, cerebral and peripheral artery disease as well as arterial fibrillation) was present in half of the patients. Most patients

were taking antihypertensive drugs, loop diuretics, phosphate binders, vitamin D3 and other vitamins, sodium bicarbonate and/or received erythropoietin.

Intervention

Training was performed on the side-alternating vibratory platform Galileo (Novotec Medical GmbH, Pforzheim/Germany). Baseline assessment of individuals' physical performance capacity and vibration exercise tolerance was assessed in a standardized manner according to the manufacturer's guidance, i.e. depending on how long individuals could tolerate a 60 degree hip width squat position at 22 Hz, they were allocated to one of three graduated training status groups with adjusted treatment intensity in terms of WBV frequency and amplitude. Accordingly, participants received one out of three predefined workout plans designated "easy", "intermediate" and "hard" depending on individual abilities. Work-out plans in terms of treatment allocation, treatment intensity (frequency/amplitude) and progression were established based on recommendations given in the manual of the device. Specific types of exercises applied as part of the training regimen were identical in all treatment groups. More specifically, exercising one leg stand on the platform was included in order to improve balance and coordination / proprioception. Frequency was increased every 4 weeks from initially 5 Hz over 7 Hz to 9 Hz. This task was performed without excursion. To improve thigh musculature function, squats were performed in 30 degree knee flexion angle with frequency gradually increased every 4 weeks from 14-18 Hz. To enhance muscular power, deep squats with 60 degree knee flexion were performed with frequencies gradually increased from 22-28 Hz. In order to foster calf musculature power, subjects exercised balancing on the forefoot with frequency increasing from 22-28 Hz. The three distinct difficulty levels were characterized by different amplitudes for the different task, gradually increasing from 0.5 to 1.5 mm for the "easy" group, 1.5-2.5 mm for "intermediate" group and 2-3 mm for the group allocated to "hard" training.

Supervised training sessions were conducted twice per week with duration and intensity gradually enhancing every 4 weeks. Each exercise phase of 30 to 60 seconds was followed by 1-2 minutes of recovery time. Training duration was 5 min in the first 4 weeks, 12.5 min during week 5-8 and 20 min in the last weeks 8-12. Training was performed before dialysis session in 8 subjects and after dialysis session in 6 subjects.

Outcome parameters of functional investigations

All participants underwent a thorough physical examination at baseline. Physical assessments were conducted before and at the end of the study. Constitutional measures included weight, height, fat mass and skeletal muscle mass index (SMI) using Bioelectrical Impedance Analysis (BIA101 Anniversary, Akern, Italy). Participant's functional status was evaluated by a series of tests for physical performance, including the following:

- Short Physical Performance Battery (SPPB): Sum score reflecting results of 3 individual test procedures, each of them being rated with 1-4 points. Accordingly, maximum SPPB score is 12 points while minimum is 4 points.
 - Static Balance Tests: Side-by-Side Stand, Semi-Tandem Stand and Tandem Stand each to be held for 10 seconds (Evaluation of the postural system).
 - Gait Speed Test: Time required to walk 4 meters at usual pace.
 - Chair Rise Test (CRT) with 5 repeats: Time required to perform 5 rises from a chair to an upright position as fast as possible without using arms. This test provides information about the strength of the lower extremities.
- 6-Min Walk Test (6-MW): Quantitates the distance a subject can walk within 6 minutes time (functional capacity of the patient).
- Timed-up and go (TUG): Measures the time needed for rising from a chair and walking 3 meters, turning back to the chair and sitting.
- Jumping Mechanography (Leonardo, Novotec Medical, Pforzheim, Germany), focusing to the single-two leg jump (s2LJ) maneuver.
- Grip strength to evaluate strength of the upper extremities was assessed by an Electronic Handheld Dynamometry (DynEx1, Akern, Italy).

Biochemical markers

Blood testing was performed before treatment initiation and after completion of the study at a defined day immediately before the dialysis session. Serum and plasma were extracted and kept frozen at -80°C until analysis (Labor Limbach, Heidelberg). Parameter included blood count, creatinine, urea, calcium, inorganic phosphate, alkaline phosphatase, glucose, HbA1c, lipids, total protein and high-sensitive C-reactive protein (hs-CRP).

Patient reported outcomes

Subjective perception of exercise intervention in terms of activities of daily living and mood were assessed using established patient reported outcome questionnaires. Specifically the German Physical Activity Questionnaire 50+ (GAPQ 50+), Falls Efficacy Scale (FES) and the Geriatric Depression Scale were obtained.

Statistical data analysis

Change from baseline in the Short Physical Performance Battery was defined as being the primary endpoint of the trial. Considering a standard deviation of 1.0 point and an increase by 1.0 point to be a clinically relevant improvement, sample size calculation based on an alpha-level of 0.05, a power of 90% yielded 12 evaluable data-sets to be required. Anticipating a drop-out rate of 20%, in total 15 participants were to be enrolled.

Final analysis includes descriptive statistics delineating frequencies, mean values, and standard deviations.

Table 2. Baseline and post treatment parameters of blood pressure, heart rate and blood chemistry.

	Baseline	Post	Change %	p-value
Systolic BP (mm Hg)	131.4 ± 17.9	123.7 ± 10.8	-5.9	0.10
Diastolic BP (mm Hg)	82.6 ± 9.8	77.1 ± 7.5	-6.7	0.06
Heart rate (per min)	71.4 ± 9.0	73.2 ± 8.9	1.5	0.30
Haemoglobin (g/dl)	12 ± 0.9	11.8 ± 1.1	-2.1	0.27
Leukocytes (per nl)	8.2 ± 2.4	6.7 ± 1.2	-17.8	0.026
Monocytes (per nl)	0.62 ± 0.16	0.62 ± 0.17	0	
hs-C-reactive protein (mg/L)	9.0 ± 9.7	6.0 ± 6.9	-28.8	0.18
Creatinine (mg/dL)	8.6 ± 2.9	8.5 ± 2.8	-1.8	0.45
Urea (mg/dL)	135.1 ± 37.6	119.4 ± 35.7	-11.6	0.30
Calcium (mmol/l)	2,27 ± 0,08	2,28 ± 0,10	0,4	
Phosphate (mmol/L)	2.0 ± 0.7	1.8 ± 0.5	-6.7	0.30
Alkaline phosphatase (U/L)	81.1 ± 60.7	76.1 ± 59.3	-2.3	0.84
Total protein (g/l)	64.3 ± 4.6	64.4 ± 5.8	0.2	0.48
Glucose (mg/dl)	104.25 ± 24.77	97.75 ± 11.14	-6.2	0.42
HbA1c (Turb. %)	5.31 ± 0.38	5.33 ± 0.27	0.3	0.90

Changes from baseline as effect measure were quantified by calculating differences of the mean values. Statistical significance was determined using t-test for paired samples. Calculations were performed using SPSS 23.0.

Results

Physical performance

Based on 14 datasets available for final analysis, 12 weeks of WBV intervention led to a significant improvement in the primary endpoint SPPB total score from 9.86 to 10.57 ($p=0.035$). Considering the solitary items constituting the SPPB, we only saw marginal changes for gait speed but relevant improvements for balance testing and particularly in the time required to perform the CRT from 10.93 sec to 8.90 sec. However, as a consequence of the large variance of individual values, these tests themselves did not reach statistical significance. Subgroup analysis of SPPB outcome considering physical impairment and treatment group allocation revealed moderate improvements in those subjects with only mild limitations (Treatment groups “intermediate” + “hard”) at baseline but a substantial benefit in those subjects with severe impairment (Treatment group “easy”). Overall, there were slight improvements in the time required to perform the TUG-Test from 8.43 sec before the intervention to 8.10 sec afterwards ($p=0.18$) for all subjects. Similarly, there was an increase in the distance attained within in 6MW from 456 m to 473 m.

Using handheld dynamometry, grip strength slightly enhanced over the course of treatment. Starting from 25.36 kg, the mean value was 26.04 kg at the end-of-study visit ($p=0.33$).

Dynamic performance measures using jumping mechanography revealed a tendency to improved values.

The relative maximum power participants exerted during a single two-leg jump maneuver improved from 25.91 W/kg to 26.66 W/kg. Along with that, the so-called EFI (Esslinger Fitness Index) improved from 82.46 to 84.42 ($p=0.61$). This was largely due to a slight increase motion velocity i.e. high-speed strength, while the force applied during jumping remained unaltered. Along with that, jump height improved from a mean of 23 to 24 cm.

As compared to baseline, common parameters of body constitution including body weight, height and Body Mass Index (BMI) remained unaffected during the course of treatment. However, mean Skeletal Muscle Index (SMI) improved from 8.98 kg/m² to 9.29 kg/m². Even though this did not reach statistical significance ($p=0.85$), the proportional increase of muscle mass with at the same time unaltered body weight has to be considered a positive consequence of exercise intervention. Details of physical assessments are depicted in Table 3.

Patient reported outcome and safety

WBV intervention was well tolerated, particularly in those patients with a predialysis training. In the postdialysis training group, i.e. in those individuals that performed their exercise after dialysis session, 2 of the 6 participants elicited an intermittent decline in blood pressure, most probably due to dialysis-induced volume contraction. One participant reported muscle indurations as a consequence of WBV interventions. After pausing for 1 week, this resolved without sequelae.

Results of patient reported outcome measures revealed an amelioration in both self-perceived physical performance abilities and mood. We could see a non-significant improvement in all categories of the German Physical Activity Questionnaire (German version), GPAQ50, indicating an increase of physical activity and energy expenditure

Table 3. Baseline and post treatment parameters of physical assessments.

	Baseline	Post	Change %	p-value
SPPB Total Score (points)	9.86 ± 1.61	10.57 ± 1.16	7.2	0.035
Balance Test (points)	3.43 ± 1.09	3.79 ± 0.58	10.4	0.55
Gait Speed [m/s]	1.28 ± 0.29	1.32 ± 0.29	3.5	0.21
Chair rise, time [s]	10.93 ± 5.86	8.90 ± 3.41	-18.6	0.16
Timed up and go [s]	8.43 ± 2.98	8.10 ± 3.00	-3.9	0.18
Power /s2LJ [W/kg]	25.9 ± 10.2	26.7 ± 10.7	2.9	0.94
Jump Height [cm]	23 ± 10	24 ± 11	2.2	0.84
Handgrip Strength [kg]	25.4 ± 12.6	26.0 ± 12.6	2.7	0.32
6 Minute Walk Test [m]	456 ± 151	473 ± 144	3.8	0.18
Skeletal Muscle Index (SMI), BIA [kg/m ²]	8.98 ± 1.80	9.29 ± 1.66	3.5	0.85

in everyday activities. Along with that, results in the Falls Efficacy Scale (FES), assessing the fear of falling, improved from 20.0 to 18.9 points. Mean values in the Geriatric Depression Scale improved from 2.8 to 2.7 points.

Biochemical analysis

Comparing blood count results before and after WBV intervention, there was no significant alteration of hemoglobin levels but we observed a significant reduction in white cell number from 8,200 to 6,700/ μ l ($p=0.026$). This was paralleled by a decrease of mean hs-CRP levels from 9.0 to 6.0 mg/l. Due to the small sample size along with large variance, reduction of this latter parameter, did not reach statistical significance ($p=0.18$).

Serum values for creatinine did not change, while urea levels showed a trend to lower values. Serum calcium levels did not change, but there was slight, non-significant decrease of phosphorous-levels. Similarly, alkaline phosphatase showed a trend to lower values in some patients. From a metabolic perspective, HbA1c levels as well as HDL levels remained unaffected. Average LDL levels diminished slightly from 106.7 to 98.4 mg/dl. Details about key lab results are given in Table 2.

Discussion

To the best of our knowledge, this is the first study evaluating the efficacy of WBV exercise in hemodialysis patients. After a treatment period of 2 sessions per week over 12 weeks, we found a trend to favorable effects. The primary outcome parameter SPPB Total Score improved significantly, particularly due to considerable betterment of the CRT, while changes pertaining to balance test and gait speed were only moderate. This appears conclusive, reflecting that vibration exercise aims at enhancing muscle power and the movement of rising from a chair is highly dependent on power, while this is not the case for walking on a flat surface or even balance. Even more, it is encouraging that results of further tests of physical performance, including the TUG and the 6MW Test

indicate a positive trend. Even though the training addressed the lower extremities, this also applied to evaluation of handgrip strength.

From a constitutional perspective, the outcome is also quite in line with what could have been expected. Working with a moderate muscle-strengthening exercise, we did not observe significant changes for both, total body weight and Skeletal Muscle Index (SMI).

Noteworthy, the responses to WBV training appeared most pronounced in those participants with lowest physical performance at baseline. This is in line with a previous observation²¹ also showing distinct improvements in severely compromised MHD patients following an active exercise program. Our results support the idea that WBV training may be an effective intervention to prevent or reverse poor muscle quality in ESRD patients. In this respect our data are in line with the results of WBV training in various other disease states such as Parkinson's disease¹⁹, Stroke²⁰ as well as in elderly subjects²²⁻²⁴.

Similar to active exercise, WBV training may exert anti-inflammatory effects²⁵. Correspondingly, we observed that WBV vibration modulated parameters of inflammation. There was a significant decline in white cell counts and an insignificant decline of hs-CRP values, suggesting an anti-inflammatory effect of WBV. However, we cannot exclude spontaneous alterations of leukocytes and hs-CRP since particularly the latter shows high variability in ESRD²⁶.

As compared to conventional endurance and resistance exercise, the cardiovascular effects of WBV training are moderate. However, WBV in short-term increases blood flow velocity and decreases arterial stiffness of the lower limbs^{14,27}. In the long range, it was demonstrated to improve cardiovascular fitness in elderly subjects²⁸. In most studies, blood pressure and heart rate were not modulated. However, in overweight/obese women prolonged WBV training improved arterial function and could even be shown to lower elevated blood pressure and heart rate²⁹. In line with that, there was a mild decline of systolic and diastolic blood pressure values while heart rate remained unchanged. Still, considering

natural variations of blood pressure levels, it remains elusive to what extent this is due to WBV intervention within this trial.

Since WBV training was shown to exert beneficial effects on carbohydrate metabolism in diabetic patients^{30,31}, we also followed the concentration levels of HbA1c but we could not observe any effect towards that parameter.

In end-stage renal disease, parameters of impaired physical performance (SPPB Total Score, 6-min walk test, timed- up and go test) as well as systemic inflammation are associated with increased all-cause mortality³²⁻³⁴. Accordingly, it is conceivable that positive effects of Whole-Body-Vibration could be associated with an improved clinical outcome in the long range.

Summing up, from the current perspective, it is unquestionable that conventional endurance and resistance exercise offer best training options to improve muscle wasting and dysfunction as well as cardiovascular function, even and especially for maintenance hemodialysis patients. However, reflecting the real life situation with a large proportion of MHD patients not finding access to conventional exercise programs, low-threshold exercise intervention on a vibration plate could provide a valuable complementary or alternative means of exercise that can also be offered to those patients unable or unwilling to perform conventional training. The advantages of WBV result from the combination of hardly any physical stress for the participants, short duration of intervention and a comparatively high effectiveness.

Major limitations of the study presented here surely are the small number of participants and the lack of a control group. Therefore, it would be premature to draw definite conclusions or give general recommendations. Still, our results can be considered a starting point in order to encourage further, larger-scale investigations with longer duration in order to verify supposed beneficial effects of WBV in maintenance hemodialysis patients.

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