BMJ Open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-008709
Article Type:	Research
Date Submitted by the Author:	07-May-2015

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Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Sports and exercise medicine
Keywords:	Nephrology < INTERNAL MEDICINE, Rehabilitation medicine < INTERNAL MEDICINE, Dialysis < NEPHROLOGY, End stage renal failure < NEPHROLOGY, SPORTS MEDICINE

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Long-term follow-up of chronic kidney disease patients performing regular exercise during hemodialysis

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Abstract

Objective: Long-term follow-up studies regarding the effect of a structured physical exercise program (SPEP) during hemodialysis (HD) assessing compliance and clinical benefit are missing.

Study Design: Single-center clinical trial, non-randomized, investigating 46 HD patients (63.2±16.3 yrs, male/female 24/22, dialysis vintage 4.4 yrs) performing an SPEP over 5 years. The SPEP (twice/week for 60 min during hemodialysis) consisted of a combined resistance (8 muscle groups) and endurance (supine bicycle ergometry) training. Exercise intensity was continuously adjusted to improvements of performance testing. Changes in endurance and resistance capacity, physical functioning and quality of life (QoL) were analysed over one year as well as long-term adherence and economics of the program over 5 years. Average power per training session, maximal strength tests (maximal exercise repetitions/min), and three performance-based tests for physical function, SF36 for QoL were assessed after 1, 6 and 12 months.

Results: 78% of the patients completed the program after 1 yr and 43% after 5 yrs. Participants were divided - according to adherence to the program - in three groups: 1.) high adherence group (HA, >80% of 104 training sessions within 12 months), 2.) moderate adherence (MA, 60-80%), and 3. Low adherence group (LA, <60%)) with HA and MA evaluated quantitatively. One-year follow-up data revealed significant ($p<0.05$) improvement for both groups in all measured parameters: exercise capacity (HA: 55%, MA: 45%), strength (HA: >120%, MA: 40%-50%), QoL in three scores of SF36 subscales and physical function in the three tests taken between 11% and 31%. . Moreover, a quantitative correlation analysis revealed a close association (r=0.8) between large improvement of endurance capacity and weak physical condition (HA).

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Conclusion: The exercise program described here improves physical function significantly and can be integrated into hemodialysis-routine with high long-term adherence.

Strengths and limitations of this study

- This study shows to the first time, that a structured, individual combined cardiovascular and resistance excercise program during dialysis, suitable also for older and frail patients, can be permanently integrated into the dialyis routine of a standard dialysis unit.

- With patients' adherence maintained at the 80% level, the improvement of strength and endurance as well as Quality of life over one year was significant and largest in very weak patients.

- With declining health status and sample size reduction due to death or transplantation the size of the cohort was too small for quantitative analysis after five years.

- The study was non-randomized.

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Introduction

Patients with end stage renal disease (ESRD) are characterized by low levels of physical activity and a continuous decline in physical function. Observational studies [1-3] have revealed that physical inactivity is associated with increased mortality in these patients. Especially during the period before and after initiation of dialysis, patients have a substantial and sustained decline in functional status in addition to a dramatically high mortality [4].

Among the many reasons for low levels of physical activity in ESRD, three factors contribute most: (i) Reduced muscle strength caused by muscle catabolism and wasting [5-7], (ii) a substantially increased cardiovascular risk in combination with a high prevalence of comorbid disorders[8], both leading to a reduced health related quality of life (QoL) [9;10], which is in itself part of a vicious cycle further impairing physical activity with subsequently (iii) reduced physical fitness.

All these factors can be improved by exercise training: Aerobic endurance exercise training in patients with ESRD has been shown to improve physical functioning and QoL [11-21], data which has been previously reviewed [22-24]. Also resistance training has been proven to increase muscle strength and physical functioning in these patients [22;25-27]. Moreover, exercise training improves cardiovascular risk factors such as blood pressure [28;29] and lipid profiles [30] as well as dialysis efficacy [31-33].

Despite these proven benefits a structured physical exercise program (SPEP) for dialysis patients is rarely performed on a routine basis. Even more scarce is regular exercise training *during* hemodialysis. This is surprising, as this approach offers a supervised setting for the patients, is time sparing as patients will not have to attend additional exercise sessions, and does even improve dialysis efficacy.

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Therefore, empirical data on short and long-term follow-up including adherence and clinical benefit is mandatory to implement this approach into routine clinical practice [34-36]. In our present study we could demonstrate that this approach is indeed feasible and can be implemented in the daily dialysis routine. This is supported by a quantitative evaluation of all data taken over the first year and detailed adherence data after 5 years.

Subjects and Methods

Subjects

Participants for the study were recruited from an outpatient hemodialysis unit (KfH, Bischofswerda, Germany), where they had been on maintenance hemodialysis for at least three months when starting the study. Patients were dialyzed three times a week for 4-5 hours and had to be in a stable medical condition (see Table 1 for patient characteristics). Patients suffering from symptomatic ischemic heart disease, orthopedic or musculoskeletal problems interfering with exercise training were excluded. 46 patients (61% of all 72 patients in the unit at the beginning of the study, 24 male) were included. Informed consent was obtained from all participants and the study was approved by the Human Research Ethics Committee at the Saxony Physician Chamber (Sächsische Landesärztekammer) Dresden, Germany.

Study design

The program of combined endurance and resistance training (30 min each per training session, design is shown in Fig. 1) started after 5 min warm-up and was performed twice a week during the first 2 hours of dialysis under direct supervision of an experienced exercise specialist. Regular maximal exercise tests provided new individual baseline

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parameters for the next training interval, namely maximal training heart and repetition rate for endurance and resistance, respectively.

Endurance Training

Endurance training was performed with bed-cycle ergometers (MOTOmed letto2, Reck MOTOmed®, Germany) positioned in front of the patients' chairs. Average power, total work and distance cycled as well as the duration of each training session was stored on a personalized memory card.

All patients were connected to a heart rate monitor with continuous registration during exercise. Each patient's target heart rate was calculated by Karvonen's method [37] from maximal exercise stress testing before inclusion into the study and stored on the memory card. The target-heart rate was derived (see Fig.1) from the maximum heart rate determined during the *maximum exercise test:* participants underwent maximal incremental exercise on a non-dialysis day using standard methodology by cycling ≥50 rpm on an electrically braked ergometer (Ergo bike therapie 2000 pc; Daum electronic, Germany) with 3 lead electrocardiogram and blood pressure monitoring. The test starts with a work load of 10 W increasing by 10 W every 2 minutes. Subjects continue until muscular fatigue, pathological electrocardiogram criteria or new clinical symptoms**.**

Resistance training

Eight muscle groups were trained with an individual target repetition rate (R) (see Fig. 1) of appropriate exercises in two sets of one minute each with a one minute break according to Table 3. Biceps and triceps were trained with weights of 0.5, 1.0, 2.0 and 4.0 kg according to patient´s strength. Similarly, for the abductor elastic bands (theraband®)

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with different resistances were used. Patients started with weights/therabands® inducing a subjectively perceived intensity of "somewhat hard".

The target-repetition rate was derived from the maximal repetition rate (MRR) in a *maximum strength test* for all 8 muscle groups: Patients were asked to perform as many repetitions as possible in one minute.

Since we observed a faster increase of the patients' strength, in modification of the training program according to Fig. 1, *maximum strength tests* for new baseline parameters and the corresponding training adaption were initiated after 3, 5, 7, and 9 months. If the MRR exceeded 50 repetitions per min a heavier weight or a more rigid theraband® with more resistance was used for the biceps/triceps or abductor exercise.

Clinical tests of physical mobility and capacity

The improvement of physical function was assessed with three performance based tests at baseline, after 6 and after 12 months:

1. The Six-minute walking test (6MWT) measures walking distance as a rough measure of maximal exercise capacity and was performed according to the American Thoracic Society [38].

2. The Timed up and go test is a short test which measures basic mobility skills [39].

3. The Sit to stand test (STS) measures functional lower extremity strength during 60s [40].

Quality of life

Quality of life (QoL) was assessed with the SF-36 survey [41] at baseline, after 6 and after 12 months.

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Motivation strategies

Patients were exercising together during dialysis and were permanently motivated by the trainer, medical staff and physicians. The individual development of exercise capacity and training data was discussed every 3 months with the patient as part of the treatment which also included the adaption of the prescribed exercise intensity.

Statistics

Quantitative analysis over one year was performed for patients who completed more than 60% of the 104 target training sessions of the first year. They were divided into a high (HA) and moderate (MA) adherence group with more than 80% and 60%-80% of the sessions completed, respectively. These groups were evaluated separately to investigate the effect of high and moderate compliance on physical functions.

The third, low adherence group (LA, <60% session participation) consisted of 5 members only, precluding follow-up evaluation due to very different comorbidities, e.g., diabetes, peripheral artery disease, cardio-vascular disease, chronical heart failure and leg amputation.

The effect of the resistance training was quantified by recording the repetitions R_N of each exercise from the *maximum exercise tests* for each patient at the beginning of training and after month 3, 5, 7, 9 and 12 months. The normalized data R_N/R_0 were compared among patients statistically to the initial value for N=0, which is by construction unity. Results including the respective p-values (ANOVA) are summarized for patient groups HA and MA in Table 3.

The success of the endurance training was assessed according to the power achieved in each training session, which was averaged over one month to give 12 data points P_N over a year for each patient. The normalized power data P_N/P_1 were compared among patients

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statistically to the initial value for N=1. Resulting curves including the p-values (ANOVA) are given for groups HA and MA in Fig. 2.

Additional analysis aimed at revealing a possible correlation between the change of power from one month to the next one, $\Delta P/\Delta t$, and the power P itself. In a typical saturation behavior for the power, characterized by a logistic equation, $\Delta P/ \Delta t$ is given by $\Delta P/ \Delta t = \alpha P(P_{\infty}-P)$, where α (in units of inverse Megajoule, MJ^{-1}) characterizes the patient's relative improvement in power for work done, while P_{∞} specifies the maximally reachable power. The relative change $Y(P) = P^{-1} \cdot \Delta P/\Delta t$ fits a linear regression curve with different slope $-\alpha$ for each patient (Fig. 3). The (linear) correlation of the slopes with the average patients' power $<P>$ is demonstrated in Fig. 4.

Quality of life and physical performance tests were quantified with paired t-test statistics.

Results

Quantitative evaluation

Strength parameters improved linearly in patients with high compliance rate (group HA) over the exercise period at *monthly* rates from 3 to 10% for all 8 muscles groups. Final results are listed in Table 3. All improvements were highly significant ($p < 0.05$).

However, strength improved considerably less in patients with a lower compliance (group MA) whose average exercise volume was about 20% less as compared to group HA (see Table 2). Significant increase ($p<0.05$) of the repetitions in the *maximum strengths tests* was only achieved towards the end of the study after 12 months and only for some of the muscle groups, namely for leg extensor, adductor, abdomen and abductor, see Table 3.

Endurance exercise capacity measured in cycling power improved for both groups HA and MA in parallel (Fig. 2). The maximal relative improvement was achieved after 3

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months and amounts to a similar increase of 55% and 45% for groups HA and MA, respectively. Correspondingly, the average power achieved in groups HA and MA differs neither at the beginning of the training (($\langle P_1 \rangle = 17.5 \pm 1.8$ W versus $\langle P_1 \rangle = 16.0 \pm 3.0$ W) nor after three months ($\langle P_3 \rangle = 22.1 \pm 2.0$ W versus $\langle P_3 \rangle = 19.4 \pm 3.2$ W). Between 3 and 12 months the endurance capacity remained the same within statistical fluctuations although with a slight trend to decrease as expected physiologically.

Figure 3 shows the relative change of power from one month to the next for patients from group HA, $Y(P) = P^{-1} \cdot dP/dt$, plotted against the power itself. Patients with a high mean power have lower slopes dY/dP (curves in the right part of the figure) than patients with a low mean power. In Figure 4 we substantiate this observation by plotting the negative slopes α from the linear regression fits in Fig. 3 against each patient's mean power $\langle P \rangle$ over the 12 month period of quantitative evaluation. A clear correlation of (α,$\langle P \rangle$) emerges with a correlation coefficient of $r=0.80$ for the linear regression shown in Fig. 4. The correlation implies that the improvement is higher in patients with a low baseline physical working capacity, a physiological phenomenon known from other conditions in healthy as well as diseased individuals. As we see here, it also holds for patients suffering from ESRD.

With the significant improvement of endurance and resistance measures, the physical function measured with three clinical tests of physical mobility improved significantly between 11% and 31%, see Table 4. Quality of life parameters improved significantly in 4 (3) subscales of SF36 after 6 (12) months, see Table 5.

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Costs for training

In a dialysis shift with exercise training, professional exercise supervision is needed for two hours corresponding to 0.1 (0.14) full time equivalent for training twice (three times) a week. In each shift a maximum of three exercising patients can share a bike. Executed in this way each training session costs approximately 8 Euro/patient, which includes financing and maintenance of the bikes.

Adherence

36 patients were still exercising after 1 year and 20 patients after 5 years. Patients' SPEP participation as well as average training intensity are shown in Table 2.

The 20 patients still participating in the program after 5 years were 68 ± 13.9 y old compared to the average of 63.2±16.3y for all 46 patients at the beginning of study. This implies that there is no bias in the age distribution of the 26 patients which terminated the SPEP. Among them were 21 forced drop-outs (13 patients died and 5 were transplanted) leaving 8 (17%) unforced drop-outs over 5 years, yielding an adherence rate of over 80%.

Discussion

Principal findings and comparison with other studies

Our individually tailored and supervised SPEP during hemodialysis led to a striking and statistically highly significant improvement of strength and endurance in the participating patients over one year. This was accompanied by an improved quality of life assessed by the SF36 questionnaire (in the subscales of physical functioning, role of physical/emotional limitations).

The unforced drop-out rate of 11 % in the first year (the other 11% drop-out patients died) was substantially lower compared to previous studies, e.g. by DePaul [17] with 50%

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drop-outs after 5 months, by Mercer et al. [16] 52% after 3 months, and by Miller et al. [28] of 60% after 6 months. We attribute this to our *combined* endurance and resistance training scheme during hemodialysis with moderate intensity in combination with a number of organizational measures to enhance the motivation for training. The quantitative improvement of strength in our patients is comparable to results reported in other studies. Van Vilsteren et al. [14] demonstrated an improvement of the lower extremities in functional tests after 3 months with combined endurance/resistance training. Likewise Oh-Park and colleagues [15] found an improved one repetition maximum of knee extension, and Johansen et al. [25] described an increased muscular strength of the quadriceps muscles. In the study by Headley et al. [27] a 12 week resistance exercise training revealed a relatively small increase of strength in leg extensors (+12.7%), and Castaneda et al. [26] showed an improvement of average strength by 32% (one repetition maximum, different muscles) over 12 weeks compared to a decline of 13% in the control who did not exercise.

It has to be emphasized that our patients trained 8 muscles groups continuously while in most other studies either the muscles were not specified explicitly or only a single group was trained. Interestingly, the improvements observed in our study are rather different between endurance and strength: For strength, the improvement is directly related to the amount of training which becomes obvious from Table 3 when comparing results for high adherence group HA and the moderate adherence group MA. This conclusion is underlined by the finding that the leg extensor is the only exercise of the MA group showing a similar significant improvement over the year as for the HA group, which can be attributed to the fact that the leg extensor is simultaneously trained in the endurance training protocol during cycling.

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The endurance improvement, on the other hand, showed no statistically significant difference between the groups (Fig. 2). Therefore, it may be concluded that endurance training twice a week with more than 60% participation over a year is sufficient to achieve the improvement documented. The endurance results also underline that the two groups HA and MA do not differ in their mean physical condition as both groups had comparable mean age and number of comorbidities (see Table 1).

The slight (statistically non-significant) decline after the maximum at month 3 (Fig. 2) has several reasons: For group HA, the key factor is motivation: it is hard to keep up over many months, in particular since the training success basically stalls after the third month. This is also corroborated by the result of the SF36 questionnaire, which reveals a slight decrease of the quality of life in the second half of the year (in subscales role of physical/emotional limitations, see Table 5). Group MA shows along with a slight decline increasing spreading of the average power towards the end of the study year, indicated by the SE in Fig. 2b. Here, often medical factors, unrelated to the training, play a role and lead to an unsteady evolution of the power data in time. Therefore, the power P_{12} achieved after month 12 in group MA does not differ significantly from P_1 at the beginning of the training despite the fact that the average level of power has been almost constant from P_3 to P_{12}.

In comparison Storer et al. [42] trained 12 patients over 10 weeks and increased the workload from 19±9W to 29±25W at the end of their study. However, only 66% of the patients completed this ambitious program. With a mean age of 44 years they were about 20 years younger than our patients and were training three times a week. While the

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absolute increase in power at which our patients cycled at the end of the study was much lower (20.8±2.6W), the relative increase by 50% was basically the same. In a number of studies the change in VO_2peak is measured to assess the success of endurance training. Although the relation to improvement in physical performance or quality of life is not yet firmly established [43], the VO_2peak increased similarly with endurance exercise as the power namely by 36% in one year [44], 22% in 10 weeks [42] and 23% in 6 months [21].

Finally, the correlation between baseline physical condition and the effect of endurance training is an important finding. In [45] it was concluded from SF-36 answers in connection with physical function tests that patients with low physical function show a larger improvement by endurance training than those with higher physical function. Complementarily, but along the same lines DePaul et al. [17] concluded that patients with high physical function show a dichotomic behavior, with no significant improvement of their health status, but improved physical impairment measures. Our analysis of α [MJ^{-1}], the relative improvement of power per work done, shows a clear anti-correlation with each patient's mean power <P> over the entire study time of 12 months in Fig. 4. This implies indeed that physically weak patients (low <P>) have a higher improvement rate (larger α) than stronger patients, a finding also known from intervention trials in healthy individuals.

We regard it as a tremendous success that after 5 years still about half of the patients participated in the SPEP with only 17% unforced drop-outs (Table 2). To the best of our knowledge there is only one published study on long-time adherence over 4 years of intradialytic training [44] with initially 24 patients who were on average 53 years old. The low number of forced drop-outs (only one patient died in 4 years) together with the relatively low average age point to a pre-selection of patients rendering the comparison to

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our study difficult. Interpreting the remaining four drop-outs as unforced and therefore relevant to determine the adherence their percentage of 17% is comparable to our unforced drop-out rate (over a 20% longer time span, namely 5 years) of also 17% (see Table 2).

Limitations of study and future research

The study was non-randomized so that comparison for non-exercising hemodialysis patients cannot be drawn. Although data on the long-term effect of SPEPs is crucial, it is difficult to assess this long impact quantitatively due to the changing and in general declining health status of the patients with time. As a consequence participating patients´ training habits significantly vary over 5 years reflected in their changing assignments to the different groups (Table 2). This is also the main reason why we have presented a quantitative evaluation in this single center study only over one year. Future study designs could differentiate the patients according to one group with stable physical condition during the study and the rest of the participating patients. The ultimate criterion for the effect of SPEPs is a reduced mortality rate which can be reliably determined over a long time span only in a much larger patient collective including a control group. This design should be realized in a multi-center study for which the present work has laid the foundation and has established a feasible and safe intervention program.

Conclusions

In conclusion, we have developed and tested a combined cardiovascular und resistance personalized exercise program which can be integrated into normal dialysis care. Patients’ strength and endurance as well as QoL improved significantly over a one-year period and adherence was close to 80% after 5 years correcting for the forced drop-outs

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related to transplantation or death. To the best of our knowledge this is the first time that an SPEP was successfully performed over half a decade. Exercise training for dialysis patients should be seen as a main strategy aside from pharmacological therapy and dialysis. It has to be titrated similarly as the dose of medication. For any medication or intervention to be effective the patient's adherence is crucial. In addition, for widespread application it must be recognized by the health insurance system. Our SPEP as described here fulfills these four criteria: Each patient receives a personally adapted training program including mode and dose. The adherence is boosted by collective training and a stimulating environment created in the dialysis unit. Last but not least, the improvement of QoL of the patients contributes to the motivation for continued or even intensified exercise training. Support of this exercise training by a German health insurance company with 8 Euros/patient/training session covers the direct costs and also contributes to the patients' motivation.

Acknowledgements

We thank all patients for long-term participation in the study and the dialysis team of the Nierenzentrum Bischofswerda for their continuous support, which was crucial for finalizing this study.

This study has been accepted as an oral presentation at the 52nd ERA-EDTA Congress, held by the European Renal Association in partnership with the UK- Renal Association London May 28-31, 2015.

Contributorship statement: KA initiated the study, KA and MH designed the study. TB and JTH were responsible for the roll out of the exercise program in the dialyis unit. TB, JTH and SK performed the constant acquisition of patient data (personal data and training data). JMR performed the analysis of patient data. KA, JMR and MH drafted the

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manuscript, RK revised it critically. All authors made critical comments, suggestions and revisions to earlier drafts. All authors interpreted results and approved the final version of the paper. KA is guarantor.

All patients who are still alive have provided their signed consent to publication

Funding: This study was funded by the "Curatorium for dialysis and renal transplantation" (KfH, non-profit dialysis provider) for the first three years, since 1/13 expenses of training have been taken over by a German health insurance company (AOKPlus Krankenkasse:
https://www.aokplus-online.de/presse/pressemitteilungen/einzelansicht/fuer-mehr-lebensqualitaet-aok-plus-bietet-ab-sofort-sporttherapie-waehrend-der-dialyse.html)
At the beginning of the study cycle ergometers were supplied by Reck MOTOmed® (RECK-Technik GmbH & Co. KG, Betzenweiler, Germany).
The KfH , the AOKPlus and Reck MOTOmed did not have any role in the study concept, design, data analysis or writing of the manuscript.

Ethical approval: The study was approved by the Ethics Committee at the Saxony Physician Chamber (Sächsische Landesärztekammer) Dresden, Germany (protocol # EK-BR-45/08-1). All participants gave informed consent before starting the study.

Transparency: KA affirms that this paper is an honest, accurate and transparent account of the study being reported, no important aspects of the study have been omitted

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous five years; no other relationships or activities that could appear to have influenced the submitted work.

Data sharing statement: No additional data available.

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Table 1: Patient characteristics

variable	group HA n=19	group MA n=12	group LA & drop outs n=15	total n=46
age (yr)	63.4 ±13.8	62.1± 18.8	63.9±18	63.2±16.3
gender, male/female	11/8	6/6	7/8	24/22
comorbidities n (percentage)				
diabetes	6 (32%)	2(17%)	9 (60%)	17 (37%)
hypertension	17 (89%)	11 (92%)	15 (100%)	43 (94%)
coronary artery disease	7 (37%)	3 (25%)	7 (47%)	17 (37%)
peripheral artery disease	5 (26%)	3 (25%)	8 (53%)	16 (35%)
cerebrovascular disease	2 (11%)	1 (8%)	5 (33%)	8 (17%)
heart failure	3 (16%)	3 (27%)	7 (47%)	13 (28%)
cancer	4 (21%)	2 (18%)	3 (20%)	9 (20%)
leg amputation	1 (5%)	0	2 (13%)	3 (7%)
BMI (kg/m2)	24.8 ± 4.7	27.6 ± 7.0	27.7 ± 6.6	27.1 ± 5.6
Kt/V	1.47±0.27	1.58 ± 0.3	1.58 ± 0.33	1.54± 0.3
dialysis vintage (yr)[a]	4 (0.3,13)	4.5 (0.3,14)	4 (1,10)	4.4 (0.3,14)
hemoglobin (g/dl)	11.52 ± 1.14	10.78 ± 1.71	11.3± 1.42	11.28± 1.4
albumin (g/dl)	39.93 ± 4.82	40.55 ± 2.28	38.24 ± 3.77	39.53±4.03

Data with a range represents mean ± SD except if noted otherwise at the beginning of the study. BMI, body mass index. Kt/V, dialysis adequacy.

[a] Results are reported as median (minimum, maximum) because of non-normal distribution

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Table 2: Patient exercise training participation

	After year 1 N [%]	After year 5 N [%]
Completers	**36 (78%)**	**20 (43%)**
group HA (80-100 % training participation) mean training participation + SE [%]:	19 (41%) 87 ± 5	15 (33%) 95± 6
group MA[a] (60-80 % training participation) mean training participation + SE [%]:	12 (26%) 71 ± 6	2 (4%) 69± 3
group LA[b] (< 60 % training participation) mean training participation + SE [%]:	5 (11%) 39 ± 14	3 (7%) 10 ± 13
drop outs	**10 (22%)**	**26 (57%)**
renal transplantation	-	5 (11%)
Death (unrelated to study)	5 (11%)	13 (28%)
other[c]	5 (11%)	8 (17%)
Total	**46 (100%)**	**46 (100%)**

"Completers" still participated in the training program after one/fives years. Training participation is given over a full 12 months in year 1 and 5, respectively. Groups HA and MA are used for quantitative evaluation after the first year, training evolution was monitored in all groups: Out of the N=15 patients of group HA in year 5, 5 (2) patients belonged to group MA (LA) in year 1. From the two patients in group MA in year 5, 1 patient belonged to group LA in year 1. From the three patients in group LA (year 5), 1(2) patients belonged to group HA (MA) in year 1.

[a] forced breaks of participation due to different medical problems;

[b] reduced participation due to long hospitalization (3 patients), long vacation (1) and lack of motivation (1);

[c] orthopedic/arthritic (4) , psychological problems (1), move to another city(1), lack of motivation (2).

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Table 3: Strength improvement through resistance training

Exercise / $(R_{12}/R_0\text{-}1)$ ±SE [%]	leg extensor	leg curl	Back	adductor	abdomen	biceps	triceps	abductor
group HA	89±15	34±10	112±31	100±21	140±32	33±7.9	47±11	129±29
p (ANOVA)	<0.0001	0.001	0.0004	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
group MA	74±22	48±30	79±58	61±32	74±32	16±15	5.6±11	43±16
p (ANOVA)	0.002	0.09	0.19	0.045	0.033	0.28	0.59	0.0007

Strength improvement R_{12}/R_0 -1 in percent measured in *maximum training tests* of all muscles trained after 12 months with respect to initial strength. The significance level p is also given. The exercises consisted of *pressing legs against big ball at the end of chair/bed* (leg extensor); *positioning a big ball under knees and squeeze it with heels* (leg curl); *hip bridge* (back); *pressing with ball* (adductor); *crunches* (abdomen); *biceps curl* (only non-shunt arm, patients were motivated to train the shunt arm between dialysis sessions); *triceps extensions* (non-shunt arm) with weights; *abductors pulling with theraband®*

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613 Table 4: Clinical tests of physical mobility

	Baseline	After 6 months	After 12 months	p 0 vs 6 months	p 0 vs 12 months
Timed up and go test [s]	10.1±4.0	9.1 ± 3.5	7.5 ± 2.8	0.002	<0.0001
Sit to stand test [repetitions/min]	16.7 ± 8.3	20.5 ± 8.8	24.2± 10.2	0.0053	<0.0001
Six minute walk test [m]	360 ± 132	374 ± 134	403 ± 141	NS	0.0002

Only patients completed all 3 test-series (24 out of 36 patients who completed the first year, all patients from groups HA/MA) were analysed. Data is expressed as mean ±SE.

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Table 5: Quality of life

	Baseline	After 6 months	After 12 months	p 0 vs 6 months	p 0 vs 12 months
Physical functioning	53 ± 37	60 ± 37	58 ± 39	0.004	0.048
Role of physical limitations	35 ± 48	50 ± 50	46 ± 50	0.005	0.033
Role of emotional limitations	51 ± 50	72 ± 45	66 ± 48	< 0.0001	0.003
Vitality	45 ± 21	50 ± 22	50 ± 27	NS	NS
Mental health	62 ± 24	67 ± 24	65 ± 27	0.014	NS
Social functioning	67 ± 27	72 ± 29	58.06 ± 34.70	NS	NS
Pain	59 ± 28	60 ± 28	56 ± 32	NS	NS
General health perception	50 ± 27	53 ± 26	42 ± 28	NS	NS

Values expressed as mean ± SD; data is from 33 out of 36 patients (completers) who answered to all 3 questionnaires.

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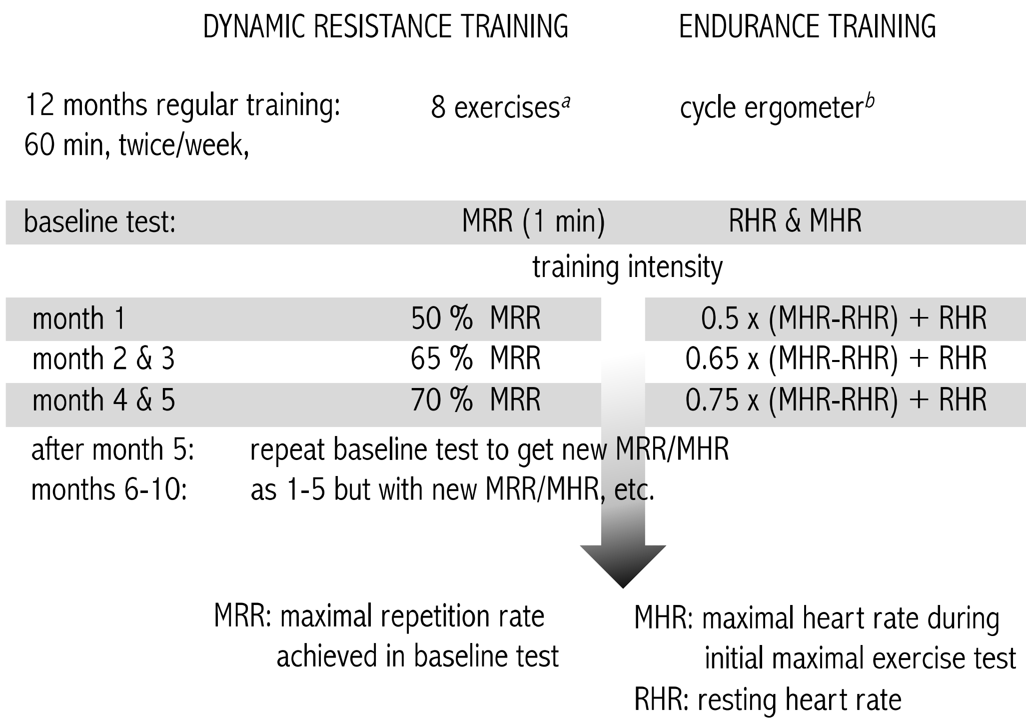

Figure 1

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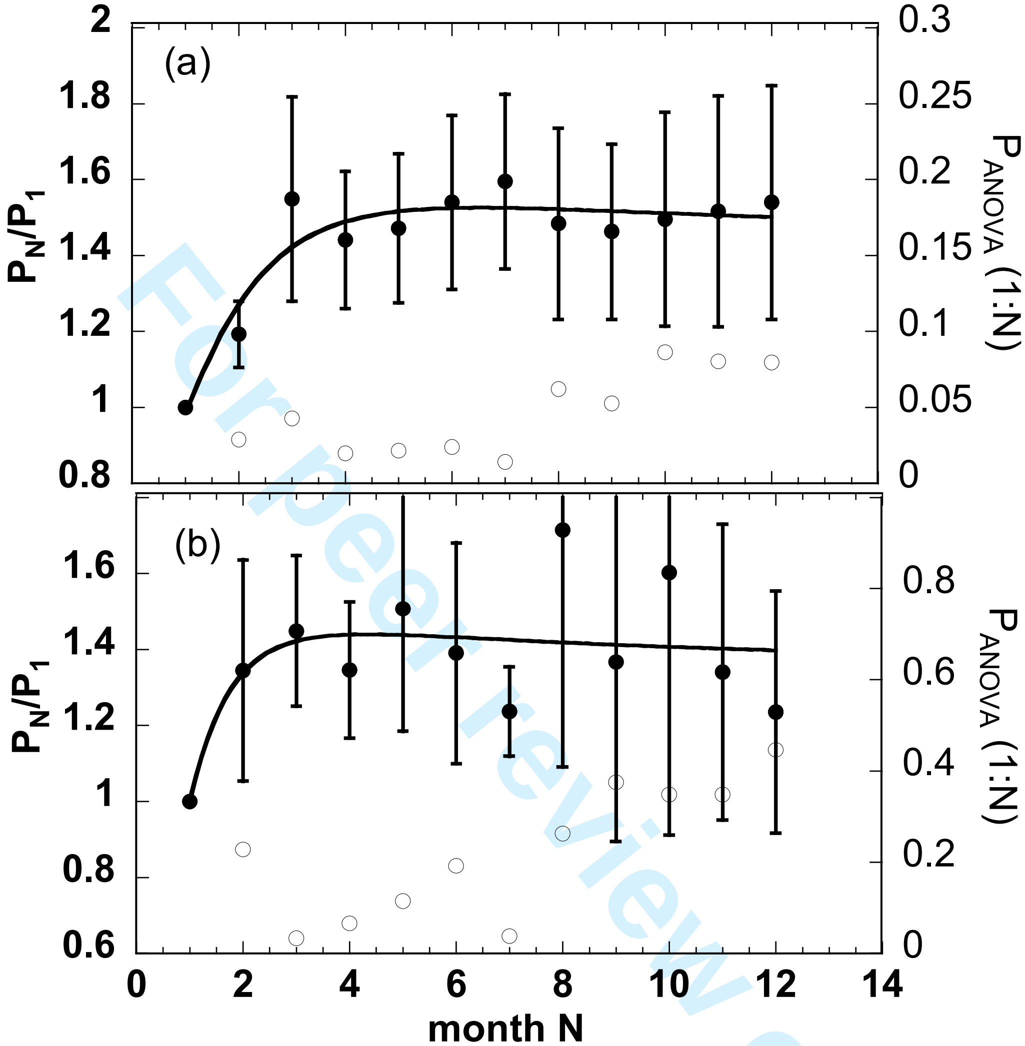

Figure 2

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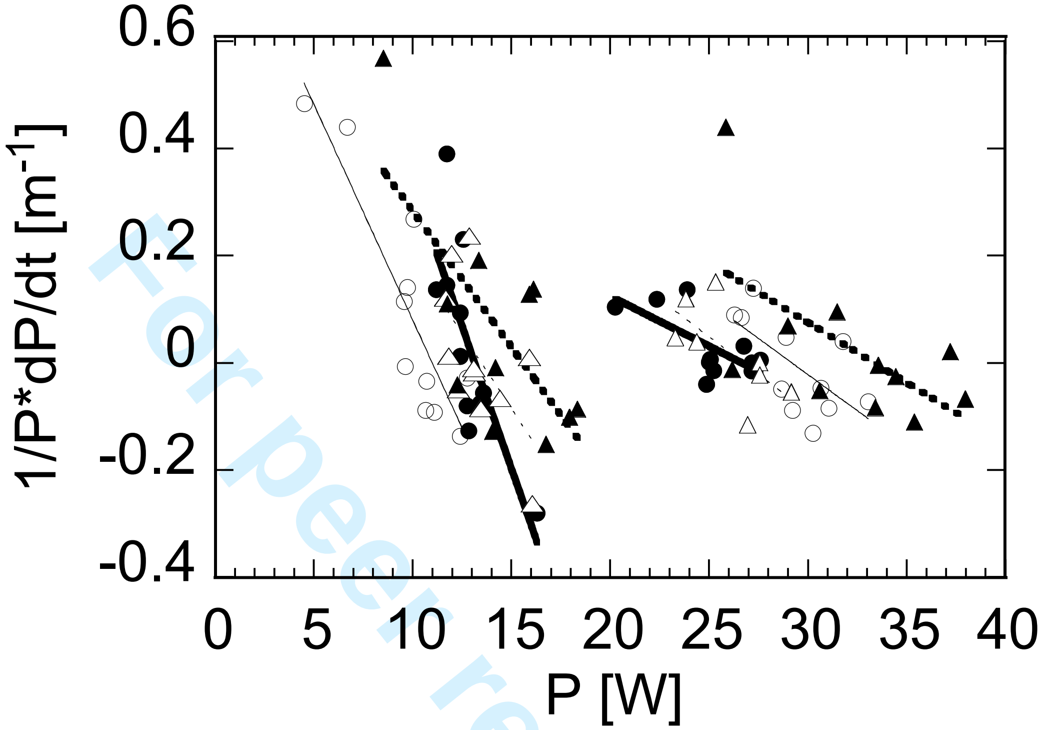

Figure 3

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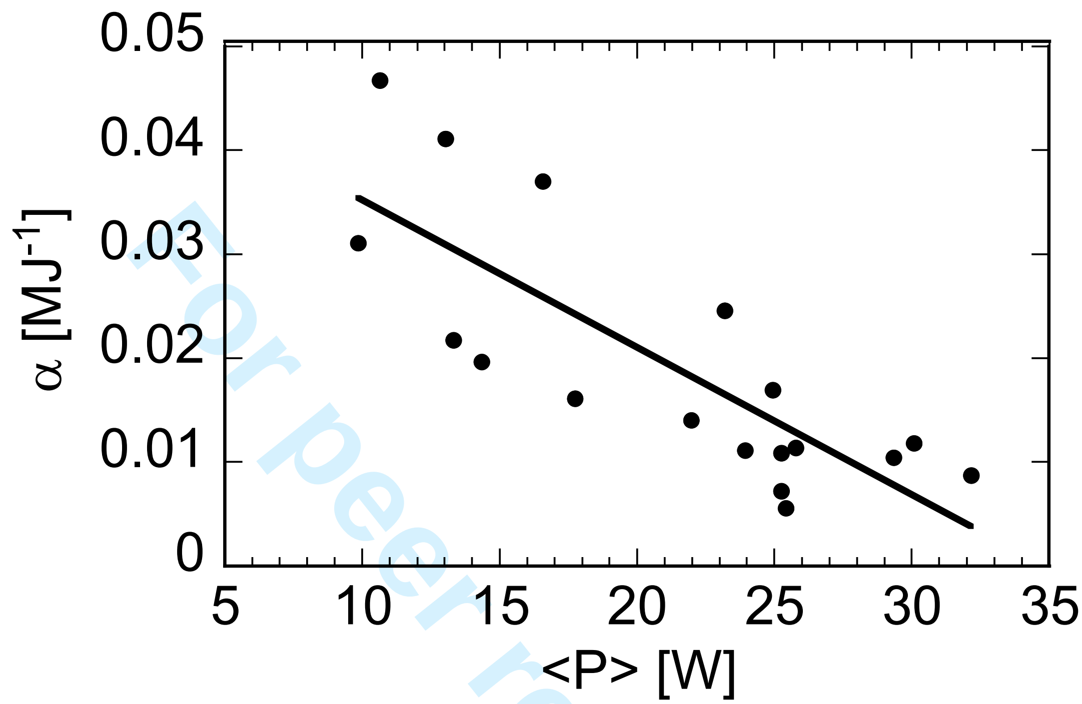

Figure 4

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Figure legends

Figure 1:

Scheme for our individual structured training to improve endurance and strength in dialysis patients including a feed-back loop. (a) The 8 exercises refer to the muscle groups biceps, triceps, abductor, adductor, abdomen, back, leg extensor and leg curl. Theraband® resistance and weights were increased in relation to the patient's training success, for details see text. (b) The training was performed with letto2 Reck MOTOmed® cycle ergometers which record automatically the exercise data, see text.

Figure 2:

Endurance built through training on the cycle ergometer according to the scheme of Fig. 1. The power P_N achieved on average in month N is shown, normalized to the power P_1 in month N=1. Data is taken from group HA and MA for part (a) and (b), respectively. The SE is given for each data point as well as the significance p(ANOVA) of P_N/P_1 being different from the initial value 1 at N=1 with the scale on the right side.

After month 3 roughly the maximum average increase is reached (55% and 45% in groups HA and MA, respectively). This corresponds to an average power of $\langle P_3 \rangle = 22.1 \pm 2.0$ W in group HA ($\langle P_3 \rangle = 19.4 \pm 3.2$ W in group MA) risen from an initial average power of $\langle P_1 \rangle = 17.5 \pm 1.8$ W and $\langle P_1 \rangle = 16.0 \pm 3.0$ W in groups HA and MA, respectively.

Figure 3:

The relative rate of change in power $Y(P) = P^{-1} dP/dt$ in two successive months as a function of the power P itself. Shown is the data of 4 patients (group HA) with a mean power of $\langle P \rangle < 15$ W and 4 patients (group HA) with $\langle P \rangle > 25$ W with individual linear regression fits.

Figure 4:

Correlation of the relative power improvement per work done, α [MJ^{-1}], work measured in Megajoule (determined from the negative slopes of the linear regression fits as in Fig. 3), and the mean power $\langle P \rangle$ for each patient from group HA.

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BMJ Open

A structured exercise program during hemodialysis for chronic kidney disease patients: Clinical benefit and long term adherence

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-008709.R1
Article Type:	Research
Date Submitted by the Author:	16-Jul-2015
Complete List of Authors:	Anding, Kirsten; Curatorium for Dialysis and Renal Transplantation, KfH Kidney Center Bischofswerda Baer, Thomas; Curatorium for Dialysis and Renal Transplantation, KfH Kidney Center Bischofswerda Trojniak-Hennig, Joanna; Curatorium for Dialysis and Renal Transplantation, KfH Kidney Center Bischofswerda Kuchinke, Simone; Curatorium for Dialysis and Renal Transplantation, KfH Kidney Center Bischofswerda Krause, Rolfdieter; ReNi-German Society of Sports Rehabilitation in CKD, Rost, Jan; Max Planck Institute for the Physics of Complex Systems, Halle, Martin; Klinikum rechts der Isar, Technische Universität München,, Department of Prevention, Rehabilitation and Sports Medicine; DZHK, partner site Munich Heart Alliance,
Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Sports and exercise medicine
Keywords:	Nephrology < INTERNAL MEDICINE, Rehabilitation medicine < INTERNAL MEDICINE, Dialysis < NEPHROLOGY, End stage renal failure < NEPHROLOGY, SPORTS MEDICINE

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A structured exercise program during hemodialysis for chronic kidney disease patients: Clinical benefit and long term adherence

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Abstract

Objective: Long-term studies regarding the effect of a structured physical exercise program (SPEP) during hemodialysis (HD) assessing compliance and clinical benefit are scarce.

Study Design: Single-center clinical trial, non-randomized, investigating 46 HD patients (63.2±16.3 yrs, male/female 24/22, dialysis vintage 4.4 yrs) performing an SPEP over 5 years. The SPEP (twice/week for 60 min during hemodialysis) consisted of a combined resistance (8 muscle groups) and endurance (supine bicycle ergometry) training. Exercise intensity was continuously adjusted to improvements of performance testing. Changes in endurance and resistance capacity, physical functioning and quality of life (QoL) were analysed over one year as well as long-term adherence and economics of the program over 5 years. Average power per training session, maximal strength tests (maximal exercise repetitions/min), and three performance-based tests for physical function, SF36 for QoL were assessed in the beginning and every 6 months thereafter.

Results: 78% of the patients completed the program after 1 yr and 43% after 5 yrs. Participants were divided - according to adherence to the program - in three groups: 1.) high adherence group (HA, >80% of 104 training sessions within 12 months), 2.) moderate adherence (MA, 60-80%), and 3. Low adherence group (LA, <60%)) with HA and MA evaluated quantitatively. One-year follow-up data revealed significant ($p<0.05$) improvement for both groups in all measured parameters: exercise capacity (HA: 55%, MA: 45%), strength (HA: >120%, MA: 40%-50%), QoL in three scores of SF36 subscales and physical function in the three tests taken between 11% and 31%. Moreover,

a quantitative correlation analysis revealed a close association (r=0.8) between large improvement of endurance capacity and weak physical condition (HA).

Conclusion: The exercise program described here improves physical function significantly and can be integrated into hemodialysis-routine with high long-term adherence.

Strengths and limitations of this study

- This study shows for the first time, that a structured, individual combined cardiovascular and resistance exercise program during dialysis, suitable also for older and frail patients, can be permanently integrated into the dialysis routine of a standard dialysis unit.

- With patients' adherence maintained at the 80% level, the improvement of strength and endurance as well as Quality of life over one year was significant and largest in very weak patients.

- With declining health status and sample size reduction due to death or transplantation the size of the cohort was too small for quantitative analysis after five years.

- Due to its study design with patient motivation being a key element, this single center study did not allow for randomization and a control group.

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Introduction

Patients with end stage renal disease (ESRD) are characterized by low levels of physical activity and a continuous decline in physical function. Observational studies [1-3] have revealed that physical inactivity is associated with increased mortality in these patients. Especially during the period before and after initiation of dialysis, patients have a substantial and sustained decline in functional status in addition to a dramatically high mortality [4].

Among the many reasons for low levels of physical activity in ESRD, three factors contribute most: (i) Reduced muscle strength caused by muscle catabolism and wasting [5-7], (ii) a substantially increased cardiovascular risk in combination with a high prevalence of comorbid disorders[8], both leading to a reduced health related quality of life (QoL) [9;10], which is in itself part of a vicious cycle further impairing physical activity with subsequently (iii) reduced physical fitness.

All these factors can be improved by exercise training: Aerobic endurance exercise training in patients with ESRD has been shown to improve physical functioning and QoL [11-21], data which has been previously reviewed [22-24]. Also resistance training has been proven to increase muscle strength and physical functioning in these patients [22;25-27]. Moreover, exercise training improves cardiovascular risk factors such as blood pressure [28;29] and lipid profiles [30] as well as dialysis efficacy [31-33].

Despite these proven benefits a structured physical exercise program (SPEP) for dialysis patients is rarely performed on a routine basis. Even more scarce is regular exercise training *during* haemodialysis. This is surprising, as this approach offers a supervised

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setting for the patients, is time sparing as patients will not have to attend additional exercise sessions, and does even improve dialysis efficacy.

Therefore, empirical data on short and long-term follow-up including adherence and clinical benefit is mandatory to implement this approach into routine clinical practice [34-36]. In our present study we could demonstrate that this approach is indeed feasible and can be implemented in the daily dialysis routine. This, together with the quantitative evaluation of all data taken over the first year constitutes the primary outcomes of the study while the detailed adherence data after 5 years form the secondary outcome, allowing for an informed estimate for the boundary conditions of a future five year quantitative study (see Supplementary Material).

Subjects and Methods

Subjects

Participants for the study were recruited from an outpatient hemodialysis unit (KfH, Bischofswerda, Germany), where they had been on maintenance hemodialysis for at least three months when starting the study. Patients were dialyzed three times a week for 4-5 hours and had to be in a stable medical condition (see Table 1 for patient characteristics). Patients suffering from symptomatic ischemic heart disease, orthopedic or musculoskeletal problems interfering with exercise training were excluded. 46 patients (61% of all 72 patients in the unit at the beginning of the study, 24 male) were included.

Informed consent was obtained from all participants and the study was approved by the Human Research Ethics Committee at the Saxony Physician Chamber (Sächsische Landesärztekammer) Dresden, Germany.

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Study design

The program of combined endurance and resistance training (30 min each per training session, design is shown in Fig. 1) started after 5 min warm-up and was performed twice a week during the first 2 hours of dialysis under direct supervision of an experienced exercise specialist. Regular maximal exercise tests provided new individual baseline parameters for the next training interval, namely maximal training heart and repetition rate for endurance and resistance, respectively.

Endurance Training

Endurance training was performed with bed-cycle ergometers (MOTOmed letto2, Reck MOTOmed®, Germany) positioned in front of the patients' chairs. Average power, total work and distance cycled as well as the duration of each training session was stored on a personalized memory card.

All patients were connected to a heart rate monitor with continuous registration during exercise. Each patient's target heart rate was calculated by Karvonen's method [37] from maximal exercise stress testing before inclusion into the study and stored on the memory card. The target-heart rate was derived (see Fig.1) from the maximum heart rate determined during the *maximum exercise test:* participants underwent maximal incremental exercise on a non-dialysis day using standard methodology by cycling ≥50 rpm on an electrically braked ergometer (Ergo bike therapie 2000 pc; Daum electronic, Germany) with 3 lead electrocardiogram and blood pressure monitoring. The test starts

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with a work load of 10 W increasing by 10 W every 2 minutes. Subjects continue until muscular fatigue, pathological electrocardiogram criteria or new clinical symptoms**.**

Resistance training

Eight muscle groups were trained with an individual target repetition rate (R) (see Fig. 1) of appropriate exercises in two sets of one minute each with a one minute break according to Table 3. Biceps and triceps were trained with weights of 0.5, 1.0, 2.0 and 4.0 kg according to patient´s strength. Similarly, for the abductor elastic bands (theraband®) with different resistances were used. Patients started with weights/therabands® inducing a subjectively perceived intensity of "somewhat hard". For illustration two short training videos are available as supplementary material.

The target-repetition rate was derived from the maximal repetition rate (MRR) in a *maximum strength test* for all 8 muscle groups: Patients were asked to perform as many repetitions as possible in one minute.

Since we observed a faster increase of the patients' strength, in modification of the training program according to Fig. 1, *maximum strength tests* for new baseline parameters and the corresponding training adaption were initiated after 3, 5, 7, and 9 months. If the MRR exceeded 50 repetitions per min a heavier weight or a more rigid theraband® with more resistance was used for the biceps/triceps or abductor exercise.

Clinical tests of physical mobility and capacity

The improvement of physical function was assessed with three performance based tests at baseline and subsequently every 6 months:

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1. The Six-minute walking test (6MWT) measures walking distance as a rough measure of maximal exercise capacity and was performed according to the American Thoracic Society [38].

2. The Timed up and go test is a short test which measures basic mobility skills [39].

3. The Sit to stand test (STS60) measures functional lower extremity strength during 60s [40].

Quality of life

Quality of life (QoL) was assessed with the SF-36 survey [41] at baseline, after 6 and after 12 months.

Motivation strategies

Patients were exercising together during dialysis and were permanently motivated by the trainer, medical staff and physicians. The individual development of exercise capacity and training data was discussed every 3 months with the patient as part of the treatment which also included the adaption of the prescribed exercise intensity.

Statistics

Quantitative analysis over one year was performed for patients who completed more than 60% of the 104 target training sessions of the first year. They were divided into a high (HA) and moderate (MA) adherence group with more than 80% and 60%-80% of the

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sessions completed, respectively. These groups were evaluated separately to investigate the effect of high and moderate compliance on physical functions.

The third, low adherence group (LA, <60% session participation) consisted of 5 members only, precluding follow-up evaluation due to very different comorbidities, e.g., diabetes, peripheral artery disease, cardio-vascular disease, chronical heart failure and leg amputation.

The effect of the resistance training was quantified by recording the repetitions R_N of each exercise from the *maximum exercise tests* for each patient at the beginning of training and after month 3, 5, 7, 9 and 12 months. The normalized data R_N/R_0 were compared among patients statistically to the initial value for N=0, which is by construction unity. Results including the respective p-values (ANOVA) are summarized for patient groups HA and MA in Table 3.

The success of the endurance training was assessed according to the power achieved in each training session, which was averaged over one month to give 12 data points P_N over a year for each patient. The normalized power data P_N/P_1 were compared among patients statistically to the initial value for N=1. Resulting curves including the p-values (ANOVA) are given for groups HA and MA in Fig. 2.

Additional analysis aimed at revealing a possible correlation between the change of power from one month to the next one, $\Delta P/\Delta t$, and the power P itself. In a typical saturation behavior for the power, characterized by a logistic equation, $\Delta P/\Delta t$ is given by $\Delta P/\Delta t = \alpha P(P_\infty - P)$, where α (in units of inverse Megajoule, MJ^{-1}) characterizes the patient's relative improvement in power for work done, while P_∞ specifies the maximally

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reachable power. The relative change $Y(P) = P^{-1}\square\Delta P/\Delta t$ fits a linear regression curve with different slope $-\alpha$ for each patient (Fig. 3). The (linear) correlation of the slopes with the average patients' power $<P>$ is demonstrated in Fig. 4.

Quality of life and physical performance tests were quantified with paired t-test statistics.

Results

Quantitative evaluation

Strength parameters improved linearly in patients with high compliance rate (group HA) over the exercise period at *monthly* rates from 3 to 10% for all 8 muscles groups. Final results are listed in Table 3. All improvements were highly significant ($p < 0.05$).

However, strength improved considerably less in patients with a lower compliance (group MA) whose average exercise volume was about 20% less as compared to group HA (see Table 2). Significant increase ($p<0.05$) of the repetitions in the *maximum strengths tests* was only achieved towards the end of the study after 12 months and only for some of the muscle groups, namely for leg extensor, adductor, abdomen and abductor, see Table 3.

Endurance exercise capacity measured in cycling power improved for both groups HA and MA in parallel (Fig. 2). The maximal relative improvement was achieved after 3 months and amounts to a similar increase of 55% and 45% for groups HA and MA, respectively. Correspondingly, the average power achieved in groups HA and MA differs neither at the beginning of the training (($<P_1> = 17.5\pm1.8$ W versus $<P_1> = 16.0\pm3.0$ W) nor after three months ($<P_3> = 22.1\pm2.0$ W versus $<P_3> = 19.4\pm3.2$ W). Between 3 and 12 months the endurance capacity remained the same within statistical fluctuations although with a slight trend to decrease as expected physiologically.

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Figure 3 shows the relative change of power from one month to the next for patients from group HA, $Y(P) = P^{-1} \cdot dP/dt$, plotted against the power itself. Patients with a high mean power have lower slopes dY/dP (curves in the right part of the figure) than patients with a low mean power. In Figure 4 we substantiate this observation by plotting the negative slopes α from the linear regression fits in Fig. 3 against each patient's mean power <P> over the 12 month period of quantitative evaluation. A clear correlation of (α,<P>) emerges with a correlation coefficient of r=0.80 for the linear regression shown in Fig. 4. The correlation implies that the improvement is higher in patients with a low baseline physical working capacity, a physiological phenomenon known from other conditions in healthy as well as diseased individuals. As we see here, it also holds for patients suffering from ESRD.

With the significant improvement of endurance and resistance measures, the physical function measured with three clinical tests of physical mobility improved significantly between 11% and 31%, see Table 4. Quality of life parameters improved significantly in 4 (3) subscales of SF36 after 6 (12) months, see Table 5.

We finally briefly comment on the 5 patients from the LA group (<60% adherence). These patients missed out on large parts of the training due to different reasons (see CONSORT statement in the Supplementary Material) and the scarce data taken shows that the spread of the mean power achieved in endurance training varies by a factor of 8 between the five patients. Most importantly, none of the LA group members showed a significant improvement over the 12 months, neither in endurance nor in resistance

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training. After year 5 two of these patients were forced dropouts (one died, the other moved). The fact that the residual 3 patients were in year 5 still exercising (2 in the HA group and 1 in the MA group, see caption table 2) is a - statistically not provable - indication of training benefit even for initially LA patients.

Costs for training

In a dialysis shift with exercise training, professional exercise supervision is needed for two hours corresponding to 0.1 (0.14) full time equivalent for training twice (three times) a week. In each shift a maximum of three exercising patients can share a bike. Executed in this way each training session costs approximately 8 Euro/patient, which includes financing and maintenance of the bikes.

Adherence

36 patients were still exercising after 1 year and 20 patients after 5 years. Patients' SPEP participation as well as average training intensity are shown in Table 2. Only 10 out of the 20 patients completing 5 years of training remained in stable clinical conditions during the whole study period. The other 10 patients had major medical problems, namely myocardial infarction (2 patients), serious infections (5 patients) or major operations (3 patients). The 20 patients still participating in the program after 5 years were 68 ± 13.9 y old compared to the average of 63.2±16.3y for all 46 patients at the beginning of study. This implies that there is no bias in the age distribution of the 26 patients which terminated the SPEP. Among them were 21 forced drop-outs (13 patients

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died and 5 were transplanted) leaving 8 (17%) unforced drop-outs over 5 years, yielding an adherence rate of over 80%.

Discussion

Principal findings and comparison with other studies

Our individually tailored and supervised SPEP during hemodialysis led to a striking and statistically highly significant improvement of strength and endurance in the participating patients over one year. This was accompanied by an improved quality of life assessed by the SF36 questionnaire (in the subscales of physical functioning, role of physical/emotional limitations).

The unforced drop-out rate of 11 % in the first year (the other 11% drop-out patients died) was substantially lower compared to previous studies, e.g. by DePaul [17] with 50% drop-outs after 5 months, by Mercer et al. [16] 52% after 3 months, and by Miller et al. [28] of 60% after 6 months. We attribute this to our *combined* endurance and resistance training scheme during hemodialysis with moderate intensity in combination with a number of organizational measures to enhance the motivation for training. The quantitative improvement of strength in our patients is comparable to results reported in other studies. Van Vilsteren et al. [14] demonstrated an improvement of the lower extremities in functional tests after 3 months with combined endurance/resistance training. Likewise Oh-Park and colleagues [15] found an improved one repetition maximum of knee extension, and Johansen et al. [25] described an increased muscular strength of the quadriceps muscles. In the study by Headley et al. [27] a 12 week resistance exercise training revealed a relatively small increase of strength in leg extensors (+12.7%), and Castaneda et al. [26]

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showed an improvement of average strength by 32% (one repetition maximum, different muscles) over 12 weeks compared to a decline of 13% in the control who did not exercise.

It has to be emphasized that our patients trained 8 muscles groups continuously while in most other studies either the muscles were not specified explicitly or only a single group was trained. Interestingly, the improvements observed in our study are rather different between endurance and strength: For strength, the improvement is directly related to the amount of training which becomes obvious from Table 3 when comparing results for high adherence group HA and the moderate adherence group MA. This conclusion is underlined by the finding that the leg extensor is the only exercise of the MA group showing a similar significant improvement over the year as for the HA group, which can be attributed to the fact that the leg extensor is simultaneously trained in the endurance training protocol during cycling.

The endurance improvement, on the other hand, showed no statistically significant difference between the groups (Fig. 2). Therefore, it may be concluded that endurance training twice a week with more than 60% participation over a year is sufficient to achieve the improvement documented. The endurance results also underline that the two groups HA and MA do not differ in their mean physical condition as both groups had comparable mean age and number of comorbidities (see Table 1).

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The slight (statistically non-significant) decline after the maximum at month 3 (Fig. 2) has several reasons: For group HA, the key factor is motivation: it is hard to keep up over many months, in particular since the training success basically stalls after the third month. This is also corroborated by the result of the SF36 questionnaire, which reveals a slight decrease of the quality of life in the second half of the year (in subscales role of physical/emotional limitations, see Table 5). Group MA shows along with a slight decline increasing spreading of the average power towards the end of the study year, indicated by the SE in Fig. 2b. Here, often medical factors, unrelated to the training, play a role and lead to an unsteady evolution of the power data in time. Therefore, the power P_{12} achieved after month 12 in group MA does not differ significantly from P_1 at the beginning of the training despite the fact that the average level of power has been almost constant from P_3 to P_{12}.

In comparison Storer et al. [42] trained 12 patients over 10 weeks and increased the workload from 19±9W to 29±25W at the end of their study. However, only 66% of the patients completed this ambitious program. With a mean age of 44 years they were about 20 years younger than our patients and were training three times a week. While the absolute increase in power at which our patients cycled at the end of the study was much lower (20.8±2.6W), the relative increase by 50% was basically the same. In a number of studies the change in VO_2peak is measured to assess the success of endurance training. Although the relation to improvement in physical performance or quality of life is not yet firmly established [43], the VO_2peak increased similarly with endurance exercise as the power namely by 36% in one year [44], 22% in 10 weeks [42] and 23% in 6 months [21].

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Finally, the correlation between baseline physical condition and the effect of endurance training is an important finding. In [45] it was concluded from SF-36 answers in connection with physical function tests that patients with low physical function show a larger improvement by endurance training than those with higher physical function. Complementarily, but along the same lines DePaul et al. [17] concluded that patients with high physical function show a dichotomic behavior, with no significant improvement of their health status, but improved physical impairment measures. Our analysis of α [MJ^{-1}], the relative improvement of power per work done, shows a clear anti-correlation with each patient's mean power <P> over the entire study time of 12 months in Fig. 4. This implies indeed that physically weak patients (low <P>) have a higher improvement rate (larger α) than stronger patients, a finding also known from intervention trials in healthy individuals.

We regard it as a tremendous success that after 5 years still about half of the patients participated in the SPEP with only 17% unforced drop-outs (Table 2). To the best of our knowledge there is only one published study on long-time adherence over 4 years of intradialytic training [44] with initially 24 patients who were on average 53 years old. The low number of forced drop-outs (only one patient died in 4 years) together with the relatively low average age point to a pre-selection of patients rendering the comparison to our study difficult. Interpreting the remaining four drop-outs as unforced and therefore relevant to determine the adherence their percentage of 17% is comparable to our unforced drop-out rate (over a 20% longer time span, namely 5 years) of also 17% (see Table 2).

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Limitations of study and future research

The study was non-randomized so that comparison for non-exercising hemodialysis patients cannot be drawn. Although data on the long-term effect of SPEPs is crucial, it is difficult to assess this long impact quantitatively due to the changing and in general declining health status of the patients with time. As a consequence participating patients´ training habits significantly vary over 5 years reflected in their changing assignments to the different groups (Table 2). This is also the main reason why we have presented a quantitative evaluation in this single-center study only over one year. Future study designs could differentiate the patients according to one group with stable physical condition during the study and the rest of the participating patients. Based on our results we estimate that for a quantitative study evaluating N patients over 5 years one needs an initial collective of N_{tot} = 14.4 N patients, where the factor 14.4 results from various losses. With N_{tot} corresponding to 100%, voluntary participation gives a reduction to 64%, death[1] and other drop out reasons a further reduction by 78.3%. Finally,

sufficient clinical stability to allow for quantitative training data over the entire 5 years was only give in 50% of the remaining patients. From our results we predict that N=30 is sufficient with a suitable study design (slightly modified in comparison with the present one). This brings N_{tot} to 432, which appears to be feasible for a multi-center study. Details of the estimate can be found in the Supplementary Material.

[1] Since the mortality rate among our participating patients was unusually low, we use here the average between our rate and the published rate from DOPPSdata, see Supplementary Material.

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390 The ultimate criterion for the effect of SPEPs is a reduced mortality rate, which can be reliably determined over a long time span only in a much larger patient collective including a control group. This design should be realized in a multi-center study for which the present work has laid the foundation and has established a feasible and safe intervention program.

Conclusions

In conclusion, we have developed and tested a combined cardiovascular und resistance personalized exercise program, which can be integrated into normal dialysis care. Patients' strength and endurance as well as QoL improved significantly over a one-year period and adherence was close to 80% after 5 years correcting for the forced drop-outs related to transplantation or death. To the best of our knowledge this is the first time that an SPEP was successfully performed over half a decade. Exercise training for dialysis patients should be seen as a main strategy aside from pharmacological therapy and dialysis. It has to be titrated similarly as the dose of medication. For any medication or intervention to be effective the patient's adherence is crucial. In addition, for widespread application it must be recognized by the health insurance system. Our SPEP as described here fulfills these four criteria: Each patient receives a personally adapted training program including mode and dose. The adherence is boosted by collective training and a stimulating environment created in the dialysis unit. Last but not least, the improvement of QoL of the patients contributes to the motivation for continued or even intensified exercise training. Support of this exercise training by a German health insurance

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company with 8 Euros/patient/training session covers the direct costs and also contributes to the patients' motivation.

Acknowledgements

We thank all patients for long-term participation in the study and the dialysis team of the Nierenzentrum Bischofswerda for their continuous support, which was crucial for finalizing this study.

This study has been accepted as an oral presentation at the 52nd ERA-EDTA Congress, held by the European Renal Association in partnership with the UK- Renal Association London May 28-31, 2015.

Contributorship statement: KA initiated the study, KA and MH designed the study. TB and JTH were responsible for the roll out of the exercise program in the dialysis unit. TB, JTH and SK performed the constant acquisition of patient data (personal data and training data). JMR performed the analysis of patient data. KA, JMR and MH drafted the manuscript, RK revised it critically. All authors made critical comments, suggestions and revisions to earlier drafts. All authors interpreted results and approved the final version of the paper. KA is guarantor.

All patients who are still alive have provided their signed consent to publication

Funding: This study was funded by the "Curatorium for dialysis and renal transplantation" (KfH, non-profit dialysis provider) for the first three years, since 1/13 expenses of training have been taken over by a German health insurance company (AOKPlus Krankenkasse: https://www.aokplus-online.de/presse/pressemitteilungen/einzelansicht/fuer-mehr-lebensqualitaet-aok-plus-bietet-ab-sofort-sporttherapie-waehrend-der-dialyse.html)

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At the beginning of the study cycle ergometers were supplied by Reck MOTOmed® (RECK-Technik GmbH & Co. KG, Betzenweiler, Germany).

The KfH , the AOKPlus and Reck MOTOmed did not have any role in the study concept, design, data analysis or writing of the manuscript.

Ethical approval: The study was approved by the Ethics Committee at the Saxony Physician Chamber (Sächsische Landesärztekammer) Dresden, Germany (protocol # EK-BR-45/08-1). All participants gave informed consent before starting the study.

Transparency: KA affirms that this paper is an honest, accurate and transparent account of the study being reported, no important aspects of the study have been omitted

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous five years; no other relationships or activities that could appear to have influenced the submitted work.

Data sharing statement: No additional data available.

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606
607 Table 1: Patient characteristics

variable	group HA n=19	group MA n=12	group LA & drop outs n=15	total n=46
age (yr)	63.4 ±13.8	62.1± 18.8	63.9±18	63.2±16.3
gender, male/female	11/8	6/6	7/8	24/22
comorbidities n (percentage)				
diabetes	6 (32%)	2(17%)	9 (60%)	17 (37%)
hypertension	17 (89%)	11 (92%)	15 (100%)	43 (94%)
coronary artery disease	7 (37%)	3 (25%)	7 (47%)	17 (37%)
peripheral artery disease	5 (26%)	3 (25%)	8 (53%)	16 (35%)
cerebrovascular disease	2 (11%)	1 (8%)	5 (33%)	8 (17%)
heart failure	3 (16%)	3 (27%)	7 (47%)	13 (28%)
cancer	4 (21%)	2 (18%)	3 (20%)	9 (20%)
leg amputation	1 (5%)	0	2 (13%)	3 (7%)
BMI (kg/m2)	24.8 ± 4.7	27.6 ± 7.0	27.7 ± 6.6	27.1 ± 5.6
Kt/V	1.47±0.27	1.58 ± 0.3	1.58 ± 0.33	1.54± 0.3
dialysis vintage (yr)[a]	4 (0.3,13)	4.5 (0.3,14)	4 (1,10)	4.4 (0.3,14)
hemoglobin (g/dl)	11.52 ± 1.14	10.78 ± 1.71	11.3± 1.42	11.28± 1.4
albumin (g/dl)	39.93 ± 4.82	40.55 ± 2.28	38.24 ± 3.77	39.53±4.03

608
609 The groups characterize the degree of training participation, HA: 80-100%, MA: 60-80%,
610 LA: <60%. Data with a range represents mean ± SD except if noted otherwise at the
611 beginning of the study. BMI, body mass index. Kt/V, dialysis adequacy.
612 [a] Results are reported as median (minimum, maximum) because of non-normal
613 distribution
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615 Table 2: Patient exercise training participation

	After year 1 N [%]	After year 5 N [%]
Completers	**36 (78%)**	**20 (43%)**
group HA (80-100 % training participation) mean training participation + SE [%]:	19 (41%) 87 ± 5	15 (33%) 95± 6
group MA[a] (60-80 % training participation) mean training participation + SE [%]:	12 (26%) 71 ± 6	2 (4%) 69± 3
group LA[b] (< 60 % training participation) mean training participation + SE [%]:	5 (11%) 39 ± 14	3 (7%) 10 ± 13
drop outs	**10 (22%)**	**26 (57%)**
renal transplantation	-	5 (11%)
Death (unrelated to study)	5 (11%)	13 (28%)
other[c]	5 (11%)	8 (17%)
Total	**46 (100%)**	**46 (100%)**

616

617 "Completers" still participated in the training program after one/fives years. Training
618 participation is given over a full 12 months in year 1 and 5, respectively. Groups HA and
619 MA are used for quantitative evaluation after the first year, training evolution was
620 monitored in all groups: Out of the N=15 patients of group HA in year 5, 5 (2) patients
621 belonged to group MA (LA) in year 1. From the two patients in group MA in year 5, 1
622 patient belonged to group LA in year 1. From the three patients in group LA (year 5),
623 1(2) patients belonged to group HA (MA) in year 1.
624 [a] forced breaks of participation due to different medical problems;
625 [b] reduced participation due to long hospitalization (3 patients), long vacation (1) and lack
626 of motivation (1);
627 [c] orthopedic/arthritic (4) , psychological problems (1), move to another city(1), lack of
628 motivation (2).
629

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Table 3: Strength improvement through resistance training

Exercise / $(R_{12}/R_0\text{-}1)$ ±SE [%]	leg extensor	leg curl	Back	adductor	abdomen	biceps	triceps	abductor
group HA	89±15	34±10	112±31	100±21	140±32	33±7.9	47±11	129±29
p (ANOVA)	<0.0001	0.001	0.0004	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
group MA	74±22	48±30	79±58	61±32	74±32	16±15	5.6±11	43±16
p (ANOVA)	0.002	0.09	0.19	0.045	0.033	0.28	0.59	0.0007

Strength improvement R_{12}/R_0 -1 in percent measured in *maximum training tests* of all muscles trained after 12 months with respect to initial strength. Groups characterize the degree of training participation, HA: 80-100%, MA: 60-80%. The significance level p is also given. The exercises consisted of *pressing legs against big ball at the end of chair/bed* (leg extensor); *positioning a big ball under knees and squeeze it with heels* (leg curl); *hip bridge* (back); *pressing with ball* (adductor); *crunches* (abdomen); *biceps curl* (only non-shunt arm, patients were motivated to train the shunt arm between dialysis sessions); *triceps extensions* (non-shunt arm) with weights; *abductors pulling with theraband*®

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Table 4: Clinical tests of physical mobility

	Baseline	After 6 months	After 12 months	p 0 vs 6 months	p 0 vs 12 months
Timed up and go test [s]	10.1±4.0	9.1 ± 3.5	7.5 ± 2.8	0.002	<0.0001
Sit to stand test [repetitions/min]	16.7 ± 8.3	20.5 ± 8.8	24.2± 10.2	0.0053	<0.0001
Six minute walk test [m]	360 ± 132	374 ± 134	403 ± 141	NS	0.0002

Only patients who completed all 3 test-series (24 out of 36 patients who completed the first year, all patients from groups HA/MA, i.e., with more than 60% training participation) were analysed. Data is expressed as mean ±SE.

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652 Table 5: Quality of life

653

654

	Baseline	After 6 months	After 12 months	p 0 vs 6 months	p 0 vs 12 months
Physical functioning	53 ± 37	60 ± 37	58 ± 39	0.004	0.048
Role of physical limitations	35 ± 48	50 ± 50	46 ± 50	0.005	0.033
Role of emotional limitations	51 ± 50	72 ± 45	66 ± 48	< 0.0001	0.003
Vitality	45 ± 21	50 ± 22	50 ± 27	NS	NS
Mental health	62 ± 24	67 ± 24	65 ± 27	0.014	NS
Social functioning	67 ± 27	72 ± 29	58.06 ± 34.70	NS	NS
Pain	59 ± 28	60 ± 28	56 ± 32	NS	NS
General health perception	50 ± 27	53 ± 26	42 ± 28	NS	NS

655

656

657 Values expressed as mean ± SD; data is from 33 out of 36 patients (completers) who
658 answered to all 3 questionnaires.

659

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Figure legends

Figure 1: Scheme for our individual structured training to improve endurance and strength in dialysis patients including a feed-back loop. (a) The 8 exercises refer to the muscle groups biceps, triceps, abductor, adductor, abdomen, back, leg extensor and leg curl. Theraband® resistance and weights were increased in relation to the patient's training success, for details see text. (b) The training was performed with letto2 Reck MOTOmed® cycle ergometers which record automatically the exercise data, see text.

Figure 2: Endurance built through training on the cycle ergometer according to the scheme of Fig. 1. The power P_N achieved on average in month N is shown, normalized to the power P_1 in month N=1. Data is taken from group HA (>80% training participation) and MA (60-80% training participation) for part (a) and (b), respectively. The SE is given for each data point as well as the significance p(ANOVA) of P_N/P_1 being different from the initial value 1 at N=1 with the scale on the right side.
After month 3 roughly the maximum average increase is reached (55% and 45% in groups HA and MA, respectively). This corresponds to an average power of $\langle P_3 \rangle = 22.1 \pm 2.0$ W in group HA ($\langle P_3 \rangle = 19.4 \pm 3.2$ W in group MA) risen from an initial average power of $\langle P_1 \rangle = 17.5 \pm 1.8$ W and $\langle P_1 \rangle = 16.0 \pm 3.0$ W in groups HA and MA, respectively.

Figure 3: The relative rate of change in power $Y(P) = P^{-1} \cdot dP/dt$ in two successive months as a function of the power P itself. Shown is the data of 4 patients (group HA, >80% training participation) with a mean power of $\langle P \rangle < 15$ W and 4 patients (group HA) with $\langle P \rangle > 25$ W with individual linear regression fits.

Figure 4: Correlation of the relative power improvement per work done, α [MJ^{-1}], work measured in Megajoule (determined from the negative slopes of the linear regression fits as in Fig. 3), and the mean power $\langle P \rangle$ for each patient from group HA.

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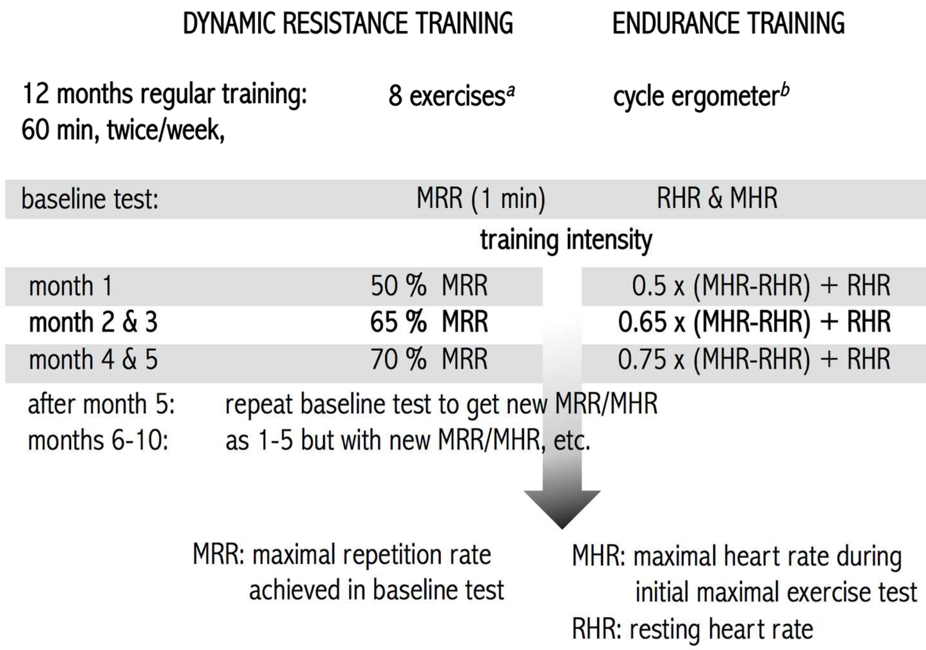

Scheme for our individual structured training to improve endurance and strength in dialysis patients including a feed-back loop. (a) The 8 exercises refer to the muscle groups biceps, triceps, abductor, adductor, abdomen, back, leg extensor and leg curl. Theraband® resistance and weights were increased in relation to the patient's training success, for details see text. (b) The training was performed with letto2 Reck MOTOmed® cycle ergometers which record automatically the exercise data, see text.
155x107mm (300 x 300 DPI)

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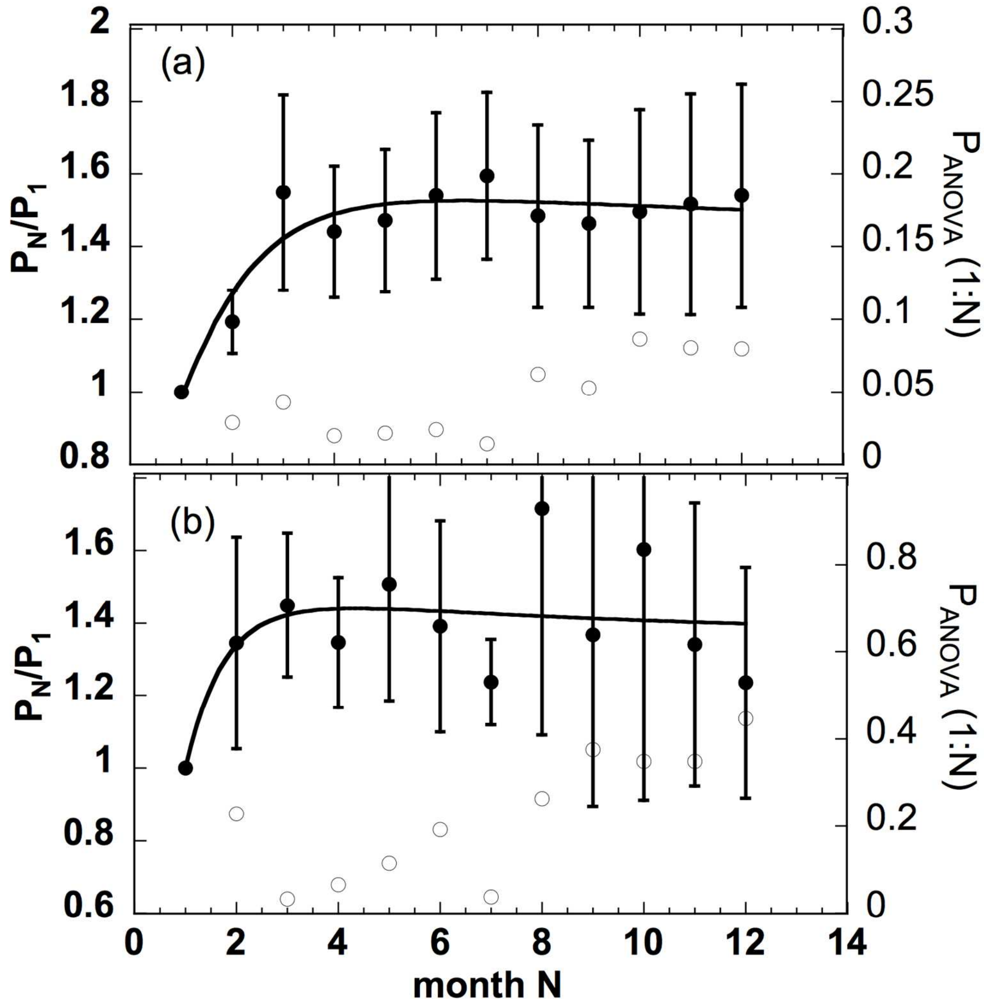

Endurance built through training on the cycle ergometer according to the scheme of Fig. 1. The power PN achieved on average in month N is shown, normalized to the power P1 in month N=1. Data is taken from group HA (>80% training participation) and MA (60-80% training participation) for part (a) and (b), respectively. The SE is given for each data point as well as the significance p(ANOVA) of PN/P1 being different from the initial value 1 at N=1 with the scale on the right side.
After month 3 roughly the maximum average increase is reached (55% and 45% in groups HA and MA, respectively). This corresponds to an average power of
<P3> = 22.1±2.0 W in group HA (<P3> = 19.4±3.2 W in group MA) risen from an initial average power of <P1> = 17.5±1.8 W and <P1> = 16.0±3.0 W in groups HA and MA, respectively.

146x152mm (300 x 300 DPI)

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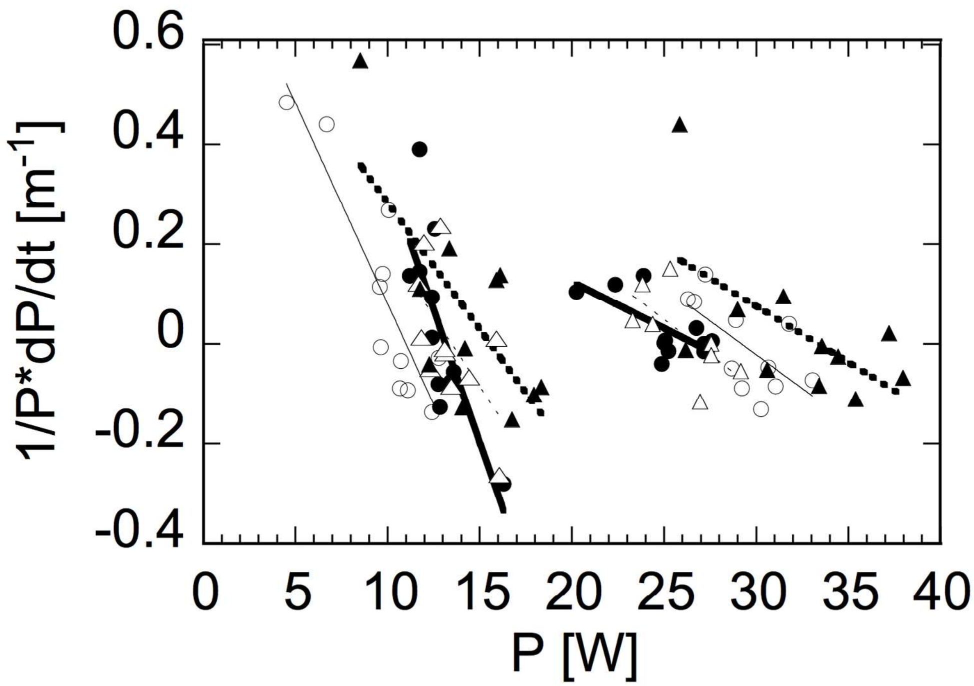

The relative rate of change in power Y(P) = P-1·dP/dt in two successive months as a function of the power P itself. Shown is the data of 4 patients (group HA, >80% training participation) with a mean power of <P> < 15 W and 4 patients (group HA) with <P> > 25 W with individual linear regression fits.
150x103mm (300 x 300 DPI)

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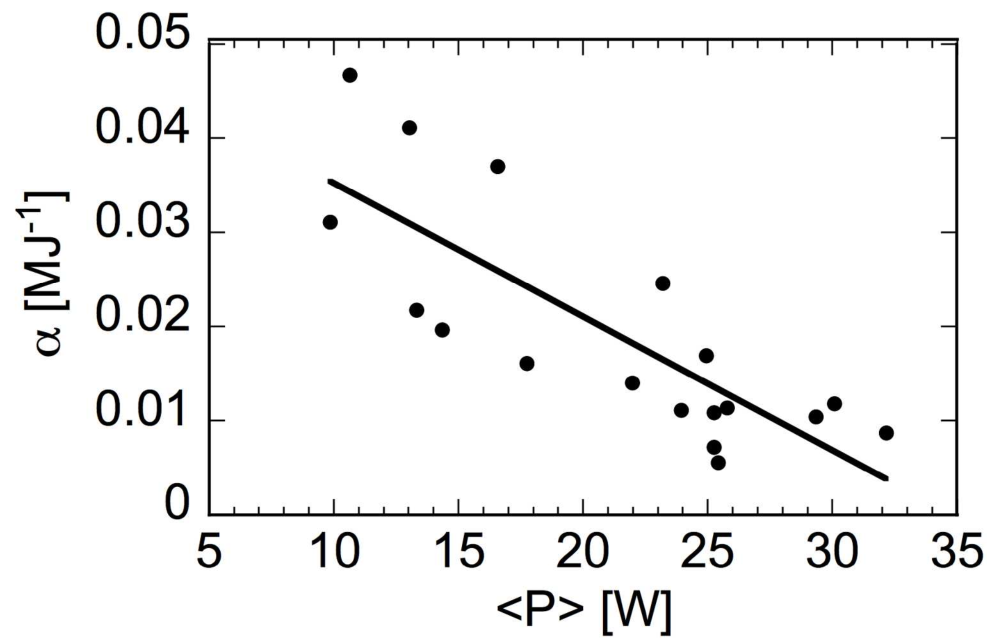

Correlation of the relative power improvement per work done, α [MJ-1], work measured in Megajoule (determined from the negative slopes of the linear regression fits as in Fig. 3), and the mean power <P> for each patient from group HA.
154x101mm (300 x 300 DPI)

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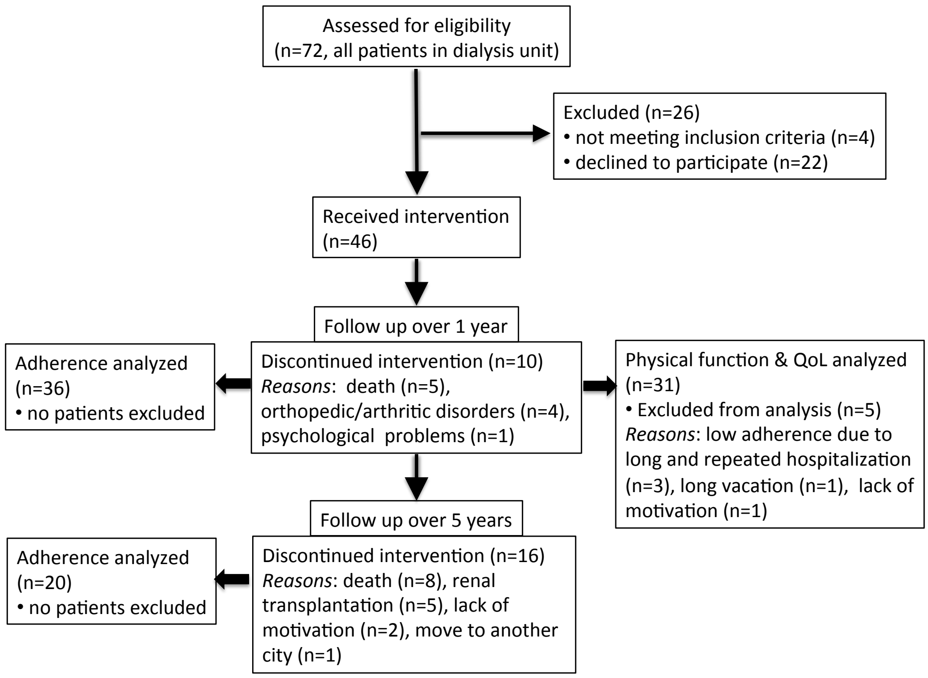
Supplementary Material for

"A structured exercise program during hemodialysis for chronic kidney disease patients: Clinical benefit and long term adherence"

by K. Anding *et al.*

1. CONSORT flow diagram



2. Estimate of initial patient collective necessary for a quantitative exercise training evaluation over 5 years

In the following we estimate the initial patient collective N_{tot} necessary to have N patients for quantitative exercise training evaluation over 5 years. The following losses are assumed to occur over the 5 year span. Numbers are given in fractions which refer to our collective.

Total drop out: 78.3%

Drop outs due to death: 50%.

Interpolating between the published mortality [15,0 deaths per 100 patient years (py) in DOPPS data, Kidney International (2014) 85, 158–165)] and the quite low mortality rate of 5.7 /100 py in our study, we assume 10 /100 py. The 10/ 100 py would correspond to 23 deaths over our 230 py of the study which would amount to 50% of our N_i= 46 of initially exercising patients.

Other drop outs: 28.3%

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In our study we have lost 13 patients (=28.3%) out of 46 due to reasons other than death.

Clinical stability: 50%

From the 20 patients still exercising after 5 years 10 were in clinically sufficiently stable condition for quantitative exercise training evaluation over the entire 5 years.

Voluntary participation: 64%

Voluntary participation has been a key element for the success of our program. Out of the $N_{tot} = 72$ patients $N_i = 46$ opted for participating in the structured exercise program.

Summarizing these factors leads the relation

$$N_{tot} = N/[(1-0.783) * 0.5 * 0.64] = 14.4\ N.$$

How large N should be depends on the details of the data one would like to retrieve. For the quantitative data we have obtained we observe a spread among the patient results over time (see increasing variance in Figure 2 of the main paper). Keeping the final patient collective N small requires a study design, which after certain time spans dynamically assigns the patients to three different training achievement categories to be pre-defined. If each category is evaluated separately, we estimate that $N = 3 * 10 = 30$ is sufficient. Without such a split of groups $N \sim 50$ appears to be a lower limit.

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