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EXERCISE & HEALTH

ASPECTS OF FATIGUE IN CHRONIC DISEASE: EFFECT OF EXERCISE TRAINING IN HEMODIALYSIS PATIENTS

by

Stefania S. Grigoriou MSc

Supervisory Team:

Dr. Giorgos K. Sakkas PhD

Dr. Christina Karatzaferi PhD

Prof. Ioannis Stefanidis MD, PhD

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«Πάντα προσπάθεια. Πάντα αποτυχία. Δεν πειράζει. Προσπάθησε ξανά. Απότυχε ξανά. Απότυχε καλύτερα».

Samuel Beckett

«Ο πολύ καλός επιστήμονας, ο πραγματικά διακεκριμένος, πιθανόν να έχει μία πρόσθετη δυνατότητα. Κυρίως αυτή η ενόραση, το θάρρος να αντιμετωπίζεις την αποτυχία. Η δυνατότητα να αποδέχεσαι την αποτυχία και να την ξεπερνάς είναι προϋπόθεση για την επιτυχία. Μάθημα πρώτον: Η αποτυχία και η επιτυχία είναι εναλλακτικές όψεις της ίδιας περίπου ζώνης. Μάθημα δεύτερον: Με έμαθε - ενώ μικρός ήμουν ανταγωνιστικός - να μην είμαι πρακτικά καθόλου ανταγωνιστικός. Μάθημα τρίτον: Δεν νοιάζομαι για το αν είμαι πιο νοήμων από τον φίλο μου... αλλά με ενδιαφέρει αν είμαι λιγότερο ή περισσότερο νοήμων από το εχθρό μου. Μάθημα τέταρτον: Συνειδητοποίησα τη σημασία της εκλογίκευσης». «Γιατί η αναζήτηση της δικής μου αλήθειας πρέπει να πατήσει στην αλήθεια του άλλου για να αποκαλυφθεί». Η έμπνευση είναι, νομίζω, να κάνεις μια σειρά συνειρμούς οι οποίοι θα προχωρήσουν ένα βήμα παραπέρα ότι έκανε ένας άλλος πριν από σένα. Σπανίως νομίζω ότι η έμπνευση στην επιστήμη έχει μοναδικότητα. Μοναδικότητα στην επιστήμη έχει η συγκυρία των περιπτώσεων».

Δημήτρης Τριχόπουλος

Abstract

Introduction: According to the National Kidney Foundation, the End Stage Renal Disease (ESRD) is a global health problem and an irreversible progressive condition responsible for high morbidity and mortality. Fatigue is experienced by many patients with a prevalence ranging from 60% to 97% and can be predictor of cardiac events. Hemodialysis (HD) patients suffer from generalized weakness, exercise intolerance and muscle atrophy, all leading to a generalized fatigue and a lack of energy. The mechanisms underlying fatigue in these patients are not well understood but from our previous work it has been shown that these should include both intramuscular and central activation failures. Recently it has been shown that the observed impaired daytime functional performance and excessive fatigue do not depend only on muscle atrophy and weakness but are also associated with other factors such as lack of restorative sleep, duration of dialysis sessions, excess weight before dialysis, poor nutritional status, restless legs syndrome and overall mental status of the patients. These factors primarily affect the HD patients' life quality, leading to a vicious circle of fatigue due to inactivity and further inactivity due to fatigue. It is evident that these patients are spending at least 50% of their time, in a functionally "switch off" mode with their fatigue sensations reaching a peak in the immediate hours after the dialysis session. As in other conditions, in ESRD as well fatigue is often viewed as having a dual nature: central vs. peripheral, brain vs. muscle, physical vs. mental etc. however it has been argued that fatigue in HD patients is more of a 'syndrome' than a single symptom with a complexity and persistence not easily relieved.

Aims: The primary aim of the current PhD research thesis was to investigate the factors involved in the phenomenon called "Hemodialysis Fatigue". More specific:

1. to investigate the role of emotional intelligence in the level of fatigue and quality of life in HD patients and whether a nine month intradialytic exercise training program could influence the levels of emotional intelligent.
2. to investigate whether a single bout of intradialytic exercise could attenuate myocardial stunning – a suspect of fatigue inducer - observed during HD session.

3. to assess the effectiveness of a nine month intradialytic exercise program on fatigue symptoms occurring before, during and after hemodialysis session in patients receiving hemodialysis therapy.
4. to investigate the effect of a nine month intradialytic exercise training program on myocardial stunning in patients on hemodialysis
5. to assess the relationship between fatigue and neural function in HD patients and whether a 9 month intradialytic exercise training program could impose any beneficial effect.

Methods: 78 dialysis patients under HD treatment (50M/28F, 60.6±17.2 years) were participated in this project.

Study 1: 78 dialysis patients under HD treatment (50M/28F, 60.6±17.2 years) were participated in the study. A subgroup of 18 patients (15M/3F, 56.7±12.3) completed a 9-month supervised intradialytic exercise training program. Functional capacity assessed by a battery of tests, while emotional intelligent, sleep quality, depression levels and daily sleepiness status were assessed via validated questionnaires, before and after the intervention period. The 78 patients were divided into 2 groups, according to their assign scores in EI scales using both WLEIS and SSEIT scales.

Study 2: A subset of twenty one stable HD patients (17M/4F, 56±19yrs) participated in the study. All participants completed two different HD trials on two different days, separated by one week: (1) normal HD and, (2) HD including a single bout of intradialytic exercise. Echocardiographic assessment of ejection fraction was completed before HD, half an hour before the end of HD and 30 min after the end of HD. Myocardial stunning was assumed when a >20% reduction in ejection fraction was observed.

Study 3: A subset of twenty stable hemodialysis patients (16M/4F, 59±13.7 yrs) was included in the study. All participants completed a 9-month supervised exercise training program during HD. Fatigue, sleep quality, depression levels and daily sleepiness status were assessed via validated questionnaires, while functional capacity assessed by a battery of tests, before and after the intervention period.

Study 4: A subset of twelve stable HD patients (10M/2F, 56±19yrs) participated in the study. All participants completed a 9-month supervised aerobic exercise training program during HD. At baseline and after 9 months in the study, all patients

underwent echocardiography assessment Echocardiographic assessment of ejection fraction was completed before HD, half an hour before the end of HD and 30 min after the end of HD. Myocardial stunning was assumed when a >20% reduction in ejection fraction was observed.

Study 5: Subsets of seventeen stable hemodialysis patients (15M/2F, 59±13.7yrs) were included in the study. All participants completed a 9-month supervised aerobic exercise training program during HD. Functional capacity assessed by a battery of tests, while pain levels and fatigue profile were assessed via validated questionnaires, before and after the intervention period. Motor and sensory nerve conduction studies on bilateral median, ulnar, peroneal and tibial nerves as well as F-wave were assessed using a full neurographic EMG system and performed pre and post exercise training program.

Results: the results of the current thesis are summarized below.

Study 1: Emotional Intelligent was positive correlated with physical health, cognitive function and levels of quality of life, while negatively associated with fatigue scores. The nine month exercise training intervention did not improve the levels of EI in the whole group, however, when patients divided according to their score of EI, the group with low score was significant improved compared to medium or high EI groups.

Study 2: Cardiac function and morphology parameters did not change after the implementation of a single bout of intradialytic exercise. Cohort data for the change in ejection fraction from baseline to during HD did mask considerable inter-individual variability however, despite this the variability was not mediated by the addition of intradialytic exercise.

Study 3: After the exercise training intervention, exercise capacity increased by 65% and functional capacity by an average of 40%. Regarding the post dialysis fatigue score, patients reported feeling better post dialysis after 9 months of exercise training program. Nine months of exercise training increased cognitive function and vitality score while depressive and fatigue symptoms were found to be significantly improved.

Study 4: Ejection Fraction improved by 21% after the 9 month exercise training intervention while at the end of the hemodialysis session were observed improvements in ejection fraction by 12% and in deceleration time by18%.

Study 5: After the nine month aerobic exercise training intervention, an significant improvement in conduction velocity observed from Tibial and Peroneal nerves by 3.7% and 4.2% respectively while Tibial F-wave latency and Peroneal and Sural nerve distal latency were significantly improved by 4.2%, 4.9% and 10% respectively. Fatigue and pain was improved after the exercise intervention while fatigue score was positively correlated with conduction velocity and amplitude values.

Discussion: In the current PhD research Thesis we have found that the levels of emotional intelligent are related to the levels of fatigue while patients with low levels of emotional intelligent are more likely to be benefited by an exercise training program compared to medium and high level counterparts (Study 1). In addition, a single bout of intradialytic exercise did not affect myocardial stunning often observed in hemodialysis patients. Our data support the notion that aerobic exercise training during hemodialysis is a safe and a well tolerable non-pharmacological approach and does not impose any harmful or adverse effect to patients' health or to the hemodialysis therapy per se (Study 2). After the 9-month aerobic exercise training program all aspects of exercise capacity were improved significantly affecting positively the levels of depression and the cognitive function of the HD patients. Post training a reduction in the severity and the duration of Post-Dialysis fatigue symptoms was observed. It seems that exercise training is a safe and effective non pharmacological approach to ameliorate fatigue symptoms in HD patients (Study 3). Following the improvements in fatigue, a significant improvement in ejection fraction by 21% was observed post training. Intradialytic exercise training can become a non-pharmacological approach to reduce myocardial stunning induced by the hemodialysis therapy (Study 4). The current study demonstrated that exercise training induces beneficial effects on both sensory and motor neural function improving conduction velocity and F-wave latency. The improvements in neural activity are accompanied by changes in fatigue score and pain related aspects (Study 5). The parallel improvement in motor nerve conduction velocity and its correlations with functional tests supports the hypothesis that exercises could be beneficial for preventing diseases-induced neuropathies in HD patients.

Conclusions: Fatigue is multifactorial condition that affects many aspects of HD patients' mental and physical health. In the current thesis we have shown that fatigue affects and is affected by emotional, cardiovascular and neurological factors that are

not fully understood. It is clear although that exercise training is a safe and low cost non-pharmacological approach that could improve many factors that are involved in the development of “hemodialysis fatigue”. Regular exercise training can reduce fatigue symptoms, revitalize cardiovascular and nervous system and significantly improve HD patients’ quality of life.

Contents

List of Tables and Images

Table 2. Echocardiographic indices of LV structure at baseline between the two different trial days.

Table 3. Echocardiographic data for loading, systolic and diastolic function at baseline, during and post dialysis in the two scenario.

Research Paper 3:

Table 1. Hemodialysis patient anthropometric characteristics, routine blood biochemistry indices and body composition values. All data are mean ± SD. No significant differences.

Table 2. Effects of 9 months exercise training on acute and subacute sense of fatigue and post-dialysis fatigue (PDF). All data are Mean ± SD.

Table 3. Effects of 9 months of aerobic exercise on cognitive function (MMSE), depressive symptoms (ZSD, BDI), chronic fatigue (FSS, MFI, BFI), emotional intelligence (WLEIS, SSEIT), pain perception (PAIN, FIQ) and quality of life indices (Physical Function, and Vitality from SF-36, and MVQOLI), sleepiness (ESS) and sleep (PSQI). All data are mean ± SD.

Research Paper 4:

Table 1. Hemodialysis patient basic characteristics before and after nine months of intradialytic exercise training.

Table 2. Heart Rate Variability indices before and after nine months of intradialytic exercise training.

Table 3. Echocardiographic indices pre and post exercise training .

Table 4. Correlations between Body Composition and Echocardiography indices.

Table 5. Correlations between Body Composition and echocardiography indices .

Table 6. Correlations between echocardiographic indices and HRV pre dialysis session.

Table 7. Correlations between echocardiographic indices and HRV during the hemodialysis session.

Table 8. Correlations between echocardiographic indices and HRV after dialysis session.

Table 9. Functional capacity data before and after the 9 month of exercise training program

Table 10. Changes in aspects related to fatigue profile before and after 9 months of intradialytic exercise training

Table 11. Correlations between patients' myocardial stunning indices and functional ability after the 9 months training

Research Paper 5:

Table 1a. Reference values of nerve compound muscle action potentials (CMAPs) parameters.

Table 1b. Reference values of sensory nerve action potentials (SNAPs) parameters.

Table 2. Hemodialysis patient basic characteristics.

Table 3. Nerve conduction assessment pre and post exercise training program.

Table 4. Functional capacity data after 9 months of exercise training program .

Table 5. Changes in aspects related to fatigue profile before and after 9 months of intradialytic exercise training.

Table 6. Correlations between patients' neurological assessment, functional ability tests and body composition indices.

List of graphs

Figure 6. Handgrip muscle strength recorded pre (in blue) and post (in red) 9 months training at different time points during 4 hrs of HD and at 30 min post dialysis (lighter symbols). Note that the value at 120 min was influenced by the preceding 60 min of exercise training. Values are presented as Mean ± S.D. * $p<0.05$ from corresponding value before the training program, ** $p<0.01$ from corresponding value before the training program.

Figure 7. Performance (repetitions) in the sit-to-stand for 30 sec (STS30) test before (in blue) and after (red) the 9 months training, before and after a dialysis session. The calculated delta difference between pre and post dialysis scores are also presented. Data are presented Mean ± SD. * $p<0.05$ from pre-training value, # $p<0.05$ from corresponding pre-dialysis value.

Figure 8. Performance (repetitions) in the sit-to-stand for 60 sec (STS60) test before (in blue) and after (red) the 9 months training, before and after a dialysis session. The calculated delta difference between pre and post dialysis scores are also presented. Data are presented Mean ± SD. * $p<0.05$ from pre-training value, # $p<0.05$ from corresponding pre-dialysis value.

Research Paper 5:

Figure 1. Changes in exercise capacity during the 9-month aerobic exercise training period. * $p<0.01$ from the pre-training values.

List of abbreviations

A: Transmitral Doppler Atrial Diastolic Wave

A': Annular Late Diastolic Myocardial Velocity

Amp: Amplitude

ANS: Autonomic Nervous System

APD: Automated Peritoneal Dialysis

BCM: Body cell mass

BDI: Beck Depression Inventory

BFI: Brief Fatigue Inventory

BMI: Body Mass Index

BNP: B-type Natriuretic Peptide

BRS: Baroreflex Sensitivity

BSA: Body Surface Area

CAPD: Continuous Ambulatory Peritoneal Dialysis

CKD: Chronic Kidney Disease

CRP: C Reactive Protein

CV: Conduction Velocity

CVD: Cardiovascular Disease

COPD: Chronic Obstructive Pulmonary Disease

D: delta

DT: Deceleration Time

E: Transmitral Doppler Early Diastolic Wave

E/A: Ratio of E and Wave Peak Velocities

E: Annular Early Diastolic Myocardial Velocity

E'/A': Ratio Of Early To Atrial Diastolic Myocardial Velocity

E/E': Ratio of Transmitral Blood Flow Velocity To Tissue Doppler Velocity

EF: Ejection Fraction

ESRD: End Stage Renal Disease

ESS: Epworth Sleepiness Scale

FIQ: Fibromyalgia Impact Questionnaire

FIS: Fatigue Impact Scale

FSS: Fatigue Severity Scale

GFR: Glomerular Filtration

IVRT: Isovolumic Relaxation Time

Hb: Hemoglobin

HCT: Hematocrit

HD: HD

HDL-C: High Density Lipoprotein Cholesterol

HF: Heart Failure

HF: High Frequency Component

HRV: Heart Rate Variability

HR: Heart Rate

KDIGO: Kidney Disease Improving Global Outcomes

L: Latency

LF: Low Frequency Component

LTM: Lean Tissue Mass

LV: Left Ventricle

LVEF: Left Ventricular Ejection Fraction

LVH: Left ventricular Hypertrophy

LVIDd: Left Ventricular Internal Diameter In Diastole

LVPWTd: Left Ventricular Posterior Wall Thickness In Diastole

IVSTd: Interventricular Septum Thickness In Diastole

MEAN RR INTERVAL: Mean Duration of All Normal To Normal Rr Intervals

MFI: Multi-Dimensional Fatigue Inventory

MMSE: Mini Mental State Exam

MVQOLI: Missoula-VITAS Quality of Life Index

NCS: Nerve Conduction Study

NO: Nitric Oxide

OEA: Emotion Appraisal Of Others

QoL: Quality of Life

pNNS0: Proportion Of Successive NN Intervals Differences>50

PNS: Parasympathetic Nervous System

PSQI: Pittsburgh Sleep Quality Index

rMSSD: Square Root of mean Squared Forward Differences of Successive Nn Intervals

ROE: Regulation of Emotion

RPE: Rating of Perceived Exertion

RRT: Renal Replacement Therapy

S: Annular Systolic Tissue Velocity

SBP: Systolic Blood Pressure

SDNN: Standard Deviation Of The Normal Rr Intervals

SEA: Self-Emotion Appraisal

SNS: Sympathetic Nervous System

SPO2: Saturation Pulse Oximetry

SSEIT: Schutte Self-Report Emotional Intelligence Test

STS: Sit-To-Stand

TBW: Total Body Water

TUG: Time Up and Go

UOE: Use off Emotion

WHR: Waist to Hip Ration

WLEIS: Wong and Law Emotional Intelligence Scale

ZSDS: Zung Self Rating Depression Scale

Introduction

Fatigue is a frequent and debilitating symptom for patients with end-stage renal disease on HD (HD) with a prevalence ranging from 60% to 97% [1-8]. Fatigue is a commonly experienced by patients as a symptom or a result of the treatment per se [9]. Approximately 86% of HD patients suffered from post-dialysis fatigue ranging from mild to severe [10]. According to Gordon and partners greater post-dialysis fatigue associated with physical inactivity of HD patients [11].

Patients on maintenance HD therapy suffered from a generalized weakness, exercise intolerance, muscle atrophy resulting in low levels of physical activity and functional capacity, all leading to generalized sense of fatigue [12, 13]. Fatigue symptoms are associated still with all cause and cardiac related mortality in HD patients [14, 15] and has been found to be predictive of cardiac events [16].

Muscle weakness, increased fatigue levels, anemia, neuropathy, low cardiorespiratory capacity, metabolic factors and exercise intolerance are some of the major factors that are reported to contribute to the low levels of functionality of the HD patients [13, 17]. Notably, the diminished functional capacity of the HD patients could result to a cascade of significant impairments on many physiological, mental and social factors which all could have a detrimental effect to the patient's quality of life (QoL) and thus to depression levels.

Furthermore, dialysis patients suffered from multiple psychosocial symptoms that have been related to fatigue including depression, health-related QoL, anxiety, loneliness, social support and suicide risk [18, 19]. Noteworthy, increased levels of fatigue are associated with high levels of depression in these patients [20].

Research findings reported that exercise intervention in general improved QoL in both clinical and health populations [21] reduced proinflammatory cytokines which have impact upon fatigue levels[22].

Many studies support the positive effect of regular physical activity on fatigue [23] and number of studies associate both aerobic and resistance exercise with

improvements in muscle structure and function, cardiac function, blood pressure, psychological adaptation and QoL [24-26].

Aims – Significance

Chronic kidney disease treated with HD, is often associated with several comorbidities like hypertension, heart diseases, musculoskeletal problems and diabetes mellitus [27, 28]. Specifically cardiovascular disease (CVD) is the leading cause of morbidity and mortality in these patients[29]. Research findings highlighted the fatigue as a predictor for CVDs in patients undergoing HD [30]. Overall, patients on dialysis have reduced exercise tolerance compared with healthy people and this physical inactivity could be a contributing factor to chronic kidney diseases (CKD). These patients present low levels of physical activity because of generalized sense of fatigue. It's very important to clarify and detect what other factors contribute to this symptom of fatigue in dialysis population.

The primary aim of the current PhD research thesis was to investigate the factors involved in the phenomenon called "Hemodialysis Fatigue". More specific:

1. to investigate the role of emotional intelligence in the level of fatigue and quality of life in HD patients and whether a nine month intradialytic exercise training program could influence the levels of emotional intelligent.
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Literature Review

Epidemiological data

Chronic renal disease is a "silent epidemic" and is emerging to be an important chronic disease worldwide [31, 32]. According to the Kidney Disease Improving Global Outcomes (KDIGO), each year 440000 patients around the world start Renal Replacement Therapy (RRT) [33, 34]. In general kidney failure is considered as one of the three death causes increasing the maximum from 1990 to 2010. According to the Institute for Health Metrics and Evaluation, in other countries such as central (Colombia, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama and Venezuela) and Andean (Bolivia, Ecuador, and Peru) the kidney failure is the fifth most common death cause [34]. According to national institute of statistic, regarding the European countries, in Italy the health research in Italy did not consider the CKD as an issue of public health and did not include it among chronic diseases [35].

Prevalence-Stages of Chronic Kidney Disease

Hebert et al. (2010) conducted a study in United States of America to compare the prevalence of the five stages of CKD across three ethnic groups (Whites, Blacks, and Hispanics) and gender in an outpatient systolic Heart Failure population. Also researchers tried to evaluate the impact of CKD on mortality. According to the authors it was more possible CKD patients to be older, as well as men were more prone to CKD, to have diabetes and higher systolic blood pressure, comparing with non-CKD patients and lower education. Finally the prevalence of CKD was higher among Hispanics and those with lesser educational attainment [36].

There are five stages of kidney disease. The determination of each stage based on the presence of kidney damage and can be described estimating the glomerular filtration rate (GFR), which is a measure of level of kidney function. Standard equations help us to evaluate the prevalence and severity of specific conditions and risk factors (hypertension, anemia, abnormalities of mineral metabolism, nutrition, QoL and measures of well-being and neurologic changes) at each stage of CKD [37].

In the early stages of kidney disease (stages 1 and 2) renal function remains sufficient to maintain the patient without symptoms. As the disease progresses, renal function decreased significantly (stages 3 and 4). At stage 5 (end stage renal failure) the kidneys are not able to perform almost any function, and their replacement is required anymore [38].

Regarding dialysis mortality stages in CKD stage 1 had the highest survival rate than patients in Stage 4 and 5 in those the survival rate was lower [36]. US and European studies enhanced the higher dialysis rate mortality with threefold and six fold higher mortality risk respectively [39].

- Comorbidities

Many CKD patients may have several comorbidities such as diabetes, CVD, metabolic bone disease, and anemia. The presence of these comorbidities leads to increase the complexity of treatment regimens [40].

Regarding the diabetes mellitus research studies indicated that 40% of CKD patients suffered from diabetes, of which three-quarters have shown proteinuria and CKD in these patients was the main cause of mortality than patients without diabetes [41]. Specifically CKD is associated with increased cardiovascular morbidity and mortality with rapidly increasing prevalence [42]. Research data reported that the prevalence of heart failure (HF) of patients commencing dialysis was between 31 and 40% [43]. Furthermore the mortality was higher in patients receiving dialysis who have comorbid HF in concrete with dialysis patients without comorbid HF [44].

It should be noted that cognitive impairment in CKD patients is another significant cause of morbidity that usually associated with lower QoL, worse survival and found difficulties to follow the medication [45]. Furthermore cerebrovascular disease is showing in all stages of CKD with increasing rate in HD patients [46].

- Life expectancy

Research studies have indicated that women had longer life expectancy than men across all levels of estimated GFR and age but the life expectancy is similar for both men and women for CKD patients with estimated GFR 15-29[47-49]. Prior studies have shown that chronic situations such as diabetes and hypertension have reduced

the life expectancy [50, 51]. Turin et al. (2012) observed that patients with lower kidney function had no so longer life expectancy divided the importance of primary and secondary prevention activities in CKD patients [52].

- Overall mental and physical health

As mentioned in previous studies identified risk factors of CKD included diabetes mellitus, hypertension, and the use of other medication however remains unknown if there are mental illnesses could be contributing to CKD. In patients receiving chronic HD has observed psychological and physical symptoms [53], most important of them including depressive symptoms and pain that contributed to impaired QoL in chronic HD patients [54].Specifically depressive symptoms were found to be related with diabetes mellitus, fatigue, limb pain and other clinical conditions [55]. Also the sleep quality observed to be impaired in HD patients and reduced the recovery time after dialysis resulting in lower QoL [56]. The association between sleep quality and depressive symptoms among HD patients seems to reduce the QoL [1, 57].

Recent research indicated that schizophrenia associated with an increased risk of CKD patients in a 3-year-follow-up period [58]. Specifically the authors have found that schizophrenia is associated with a 25% increase in the risk of developing CKD within only a 3-year follow-up period.

Studies have found that renal dysfunction associated with worse physical performance, frailty and less functional status [59]. Early studies conducted in patients with ESRD compared with healthy people have shown marked impairment in aerobic capacity and physical performance and lower physical activity

Prior small interventional trials conducted largely in ESRD patients suggest beneficial effects of structured exercise training on physical performance, cardiorespiratory fitness, and patient-reported outcomes, while a small number of trials suggest similar benefit in non-dialysis CKD patients [60, 61]

- Conservative treatment and therapy

Substitution of renal function can be done by three methods: HD, peritoneal dialysis and kidney transplantation. HD and peritoneal dialysis can partially replace the

excretory functions. The kidney transplantation only offers the possibility of full rehabilitation both extra-renal excretory and endocrine renal function [62].

1. Hemodialysis

HD is a substitution method to treat advanced and permanent kidney failure in special dialysis centers. During HD the blood be removed from the body and sent to specific filters with solutions to remove harmful substances. Specifically step-by-step description of HD has as following: The blood exits and enters in the body through the vascular access. In each session two needles are placed in access. One of the needles subtracts the "unclear" blood from the body and the other replace the blood "clear". Plastic tubes or "lines" used to transfer the blood to the HD machine. These "lines" are associated with the needles importing the vascular access of the patient. Furthermore, the blood, which is transported through the filters at constant speed, reaches the blood pump. The role of filters is the retention of retaining elements and the subtraction of extra fluids. After that the cannulated blood is returning to the body. The procedure takes about 3 - 4 hours each time and the main symptom of the patients after dialysis is the fatigue. Most of them feel tired after [63].

Although HD is the most usual RRT method the mortality of this form is increasing during the first 3 months. According to Bradbury et al. (2007) yearly mortality in dialysis emerged 5-27% in developed countries [64]. Specifically in Europe life expectancy is only 5 years, which is 50% lower than in the same age group in the general population [65].

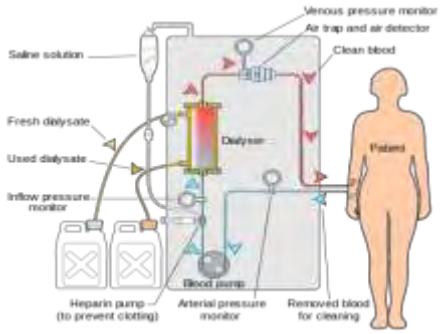
- Effect of HD on Health, QoL and EI

It is well known that the HD patients have shown usually mental, social and physical problems that that often associated with the renal disease per se or the dialysis therapy resulted in poor QoL [66, 67]. Recent studies still associated low levels of QoL with depressive symptoms in HD patients [68-70].

Regarding the HD patients, a brief review of the literature revealed that only one study examined EI in this population. Khan et partners (1971) studied social adjustment, emotional status, level of intelligence, and self-concept of fourteen children; five had transplanted kidneys that had been functioning well for periods of two to five years, two others had unsuccessful transplants, and the remaining seven

had been on HD from six months to several years. Researchers concluded that most of the children had serious social and emotional difficulties. Feelings of social isolation, excessive dependency upon the parents, and depression were common. The authors point out the sources of social and emotional difficulties and make suggestions for avoiding some of them [71].

Image 1. The process of HD (en.wikipedia.org).

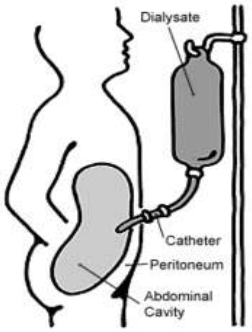


2. Peritoneal dialysis

Before the start of peritoneal dialysis is necessary to place a catheter in patient's belly by surgery. There are two kinds of peritoneal dialysis: Continuous Ambulatory Peritoneal Dialysis (CAPD) and Automated Peritoneal Dialysis (APD).

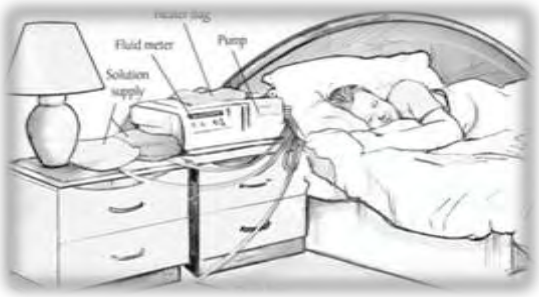
The CAPD is a "continuous, and does not require machine. It's important to be done in a clean place. The drained fluid is hooking up from a plastic bag to the tube in the belly through the catheter. The abdomen holds the dialysate with the catheter sealed. Every exchange becomes four or five times during the day and takes 30-40 minutes. Its usual patients make the exchanges at mealtimes and at bedtime. [72]

Image 2. CAPD (en.wikipedia.org).



APD needs a machine which performs 3-5 exchanges during the night. The abdomen fills automatically with dialysis solution. Furthermore this dialysis solution stays there, drains and empty to a sterile drainage bag in the morning. This method is more flexible during the day but patient can remain attached to the machine for 10 to 12 hours during the night [73].

Image 3. APD (idney.niddk.nih.gov).



3. Kidney Transplantation

Transplant surgery can be applied in patients undergoing either HD or peritoneal dialysis. During the operation the donor kidney that will be placed in the lower abdomen. The kidney artery and vein will be sutured (sewn) to the recipient's iliac artery and vein. After that the ureter of the donated kidney is connected to your bladder. During the operation a small drain may be inserted into the abdomen to drain any excess fluid that may have accumulated [74]. The donor kidney may be derived by a) living related donor (such as a parent, sibling, or child) b) living unrelated donor c) deceased donor [75].

Symptoms of Chronic Kidney Disease

It is well known that there is a broad range of symptoms in CKD. Regarding the physical symptoms most frequently these patients experienced dry mouth and itchy skin [76]. Previous studies have documented symptoms such as tiredness, pruritis, numbness, pain, and muscle cramping [77, 78].

One of the most common causes of death in CKD patients is cardiovascular events [79, 80] by the presence of predisposing factors such as hypertension, diabetes mellitus, prolonged anemia, arterial calcification and electrolyte imbalance [81]. First

of all Dr. Bright [82] reported the link between CKD and CVD indicating that impairment of renal function associated with an increasing risk of CVD[83]. Diabetes mellitus and hypotension seem to be strong risk factors that enhanced the impact of CKD in CVD risk [51, 84, 85].

Specifically, according to a recent study there is a bidirectional relationship between intradialytic hypotension and left ventricular hypertrophy in CKD patients [86]. Intradialytic hypotension namely a decrease of systolic blood pressure includes symptoms as abdominal discomfort, yawing, sighing, nausea/vomiting, muscle cramping, restlessness, dizziness or anxiety [87, 88].

Cardiovascular system

CKD is associated with increased risk for cardiovascular events and mortality. Especially ESRD who receive HD therapy experienced several cardiovascular complications such as coronary artery disease, congestive heart failure, arrhythmias and hypertension. High blood pressure, insulin resistance, dyslipidemia, vascular calcification, chronic inflammation, oxidative stress, endothelial dysfunction and other metabolic disturbances contribute to structural and functional changes in myocardium and accordingly lead to cardiac dysfunction and to increase cardiovascular events in patients with CKD.

Left ventricular hypertrophy (LVH), dilatation, systolic and diastolic dysfunction are components of the condition who is used to describe the effects of CKD on myocardium, termed as uremic cardiomyopathy leading to changes in the systemic hemodynamics affecting the structural and functional characteristics of the in myocardium. The main result of uremic cardiomyopathy is LVH which is manifested in the 26% of patients in stage 3 of CKD and in the 75% of patients on HD therapy [89] and is considered as an independent predictor of survival in CKD patients [90]. LVH is the result of hypertension and arteriosclerosis which occur due to pressure and/or volume overload that induced from anemia, arteriovenous fistula and hypervolemia in CKD patients [91] and it could be characterized as an adaptive response to these complications. Hypertension and increased volume overload, probably induce cardiomyocyte hypertrophy and vascular remodeling [92].

Additionally, an excessive activation of the renin-angiotensin-aldosterone system [93] as well as the phosphoinositide-3 kinase (PI3K)-Akt pathway contributes further to the development of LVH in these patients' population [94]. LVH also is responsible for the left ventricular dilatation and dysfunction and for the decreased left ventricular EF.

In addition other factors influence the development of cardiac diseases in CKD patients such as increased levels of homocysteine [95], hyperparathyroidism, hypoalbuminaemia, oxidative stress and inflammation. Anemia and impairment mineral metabolism, stimulate hyperphosphatemia and elevated parathyroid hormones levels leading to vascular calcification by altering the phenotype of vascular smooth muscle cells [93]. Hypovitaminosis D, which is a common disturbance of CKD patients, contributes to myocardial hypertrophy and it has been associated with cardiovascular mortality and sudden cardiac death [96]. A possible explanation is the multifactorial role of vitamin D on heart remodeling such as cardiac cell contraction, proliferation, hypertrophy, differentiation as well as protein and collagen expression [93].

CKD patients are characterized by very low levels of functional capacity which is responsible for the exercise intolerance and early fatigue that these patients experienced. Consequently, due to the reduced levels of aerobic capacity ESRD have to deal with many difficulties in performing the everyday living activities. Several factors are responsible for the low functional ability found in CKD patients. For example, VO2peak in ESRD patients is decreased by ≈50% compared to healthy age-matched values and therefore the activities of these patients are limited to those intensities require low level of aerobic capacity [97]. Limitations in oxygen delivery during exercise training due to cardiac dysfunction and complications in blood circulation are considered as the major causes for the reduced VO2peak that CKD patients present.

Painter [17], suggested that many factors interact and are responsible for the low levels of aerobic capacity seen in CKD patients, such as decreased cardiac output which is attributed to the low heart rate, low arterial oxygen content induced from anemia and abnormal muscle function which is attributed to uremic myopathy and

neuropathy. Additionally, malnutrition, impaired energy metabolism, secondary hyperathyreoidism and inactivity enhance the symptoms of uremic myopathy.

Changes induced by uremic myopathy in skeletal muscles are responsible for the muscle wasting and the preliminary fatigue in CKD patients. According to studies decreased fiber size, especially atrophy and loss of IIα and IIx fibers, reduced capillary density and peripheral activation [98] and a significant reduction in the mean diameter of both fiber types have been found in CKD patients [99]. Moreover, disturbances in mitochondrial morphology found in CKD patients possibly explain the increased fatigability [100].

Central or peripheral uremic neuropathy resulted in cardiac autonomic nervous system (ANS) dysfunction, which is a common feature in patients receiving HD therapy. A reduction in both sympathetic (SNS) and parasympathetic nervous system (PNS) occurs in uremic dysautonomia and especially parasympathetic failure during HD is a common complication in uremic patients [101]. Spectral analysis of heart rate variability (HRV) is the most commonly noninvasive method used for the assessment of ANS activity and autonomic dysfunction and is usually expressed with depressed HRV in CKD patients. In addition, HRV is considered to be an independent predictor of mortality in HD patients [102]. Decreased HRV due to dysfunction of the cardiac ANS is a known complication of HD patients and is associated with an increased risk of ventricular arrhythmias and sudden death. Furthermore, it has been reported that a sympatho-vagal imbalance in the cardiovascular system which is expressed with reduction in the indices of SDNN, LF and LF/HF ratio is related with sudden cardiac death [103]. Many studies have supported the notion that HD therapy itself induces changes in HRV of uremic patients [101, 104-107]. Specifically, it has been observed decreased sympathetic activity during HD [104] in contradiction to the results of some other authors demonstrating a shift in sympathovagal balance towards sympathetic activation during the HD process [105, 106].

Exercise training can ameliorate or delay the progress of all these consequences of CKD. Since the early ’80 many different modalities of exercise training programs have been applied in CKD patients such as home-based, habitual, center-based and intradialytic. All these studies have documented that exercise training is possible in

CKD patients, due to the hemodynamic changes inducing beneficial responses by improving functional capacity and overall health related QoL.

Fatigue in Chronic Kidney Disease

Fatigue is a complex interaction of biological and psychological factors experienced by HD patients [108] Research findings associated the fatigue with the health related QoL, depression, anxiety, loneliness, social support and suicide risk [18]. More specifically research findings have shown the close relationship between fatigue in HD patients but it's not so clear the nature of the relationship. Also the question is if an HD patient becomes depressed because of the effects of being fatigued or because of the reverse[1].

Other factors that contribute to the excessive fatigue area lack of restorative sleep [109], excess pre-dialysis weight [110], poor nutritional status [14]restless legs syndrome [111]and the overall mental status of the patients [14]. Evidently, of all of these factors can contribute to a self-exacerbating process, a vicious circle, of fatigue due to inactivity and further inactivity due to fatigue. This sensation of an enduring fatigue interferes with physical and social activities and feeds perceptions of increased restrictions and barriers [112] and leads to a significant reduction of physical activity and functional capacity, which in turn contributes to the increased cardiovascular risk and a high mortality rate among these patients [113]

Physical Activity in Chronic Kidney Disease patients

Generally, HD patients are characterized by low physical activity levels and even habitual exercise training programs might improve the functional ability of these patients (table 2). Cupisti et al [114], who evaluated the habitual physical activity levels during a mid-week interdialytic period of 48 hours in 50 ESRD patients, found that patients revealed reduced daily METs value by 14% compared to normal subjects and decreased number of steps/day by 52.4%. In addition these results were correlated with patients' dietary nutrient intake and body composition [114]. These results confirmed that malnutrition and muscle atrophy are important factors which leads to inactivity in CKD patients. However, in another study by Kosmadakis et al [115], increased exercise tolerance measured with Borg Rating of Perceived Exertion (RPE) after 1 month and 6 months exercise training was found and these beneficial effects did not get lost after 6 months of no training. In the same study [115] 6 months of

habitual exercise training weren't enough to induce changes in arterial stiffness biomarkers and baroreflex (BRS) sensitivity. The results of this study [115] indicate that habitual physical activity is not enough to induce beneficial results in the CKD patient's cardiovascular system and systematic exercise training is needed.

In another study by Matsuzawa et al [116] habitual exercise training found to be related with high density lipoprotein cholesterol (HDL-C) levels, which are related with cardiovascular mortality. The authors after examining habitual physical activity levels using accelerometers in 116 CKD patients on HD, demonstrated that increased physical activity levels were correlated with improved prognosis. Indeed, in 1980 a study by Keys [117] found that in men, low levels of HDL-C were related to coronary artery disease mortality while high levels of HDL-C to other causes of mortality. In a review by Besler et al [118], the authors described the mechanisms of how high HDL-C levels induce cardioprotective effects in the vasculature and indisputably the fact that HDL-C accelerates nitric oxide (NO) synthesis is proved to be a crucial mechanisms, which enhances the atheroprotective effects.

Moreover, a study of Hamasaki et al [119] in heart failure patients found that a correlation existed between physical activity levels and plasma BNP levels, even after an adjustment with age and BMI. B-type natriuretic peptide (BNP) is widely used as a cardiovascular risk biomarker and an increase in serum levels has been related with the degree of left ventricular dysfunction, severity of congestive heart failure symptoms and ultimately poor prognosis [118, 120], the authors described the mechanisms of how high HDL-C levels induce cardioprotective effects in the vasculature and indisputably the fact that HDL-C accelerates nitric oxide (NO) synthesis is proved to be a crucial mechanisms, which enhances the atheroprotective effects.

Most of the investigators who have examined the impact of long term exercise training on HD patients (≥6 months) have found significant improvements in psychological status [121-124]. Conversely, studies with fewer months of training such as 2 months [26], 3 months [125-129] and 4 months [130] did not find any significant improvements in depressive symptoms or in mental health scale of the SF36 with exemption of the study by Oh-Park et al [129] who reported significant improvements in MCS after 4 months of combined intradialytic aerobic and resistance

exercise training. Differences among studies in the exercise regime (duration and intensity) could be the reason for the observed discrepancies.

Even though there are no exercise studies lasting more than a year, there are strong evidences regarding the superiority of the long term exercise interventions in terms of improving psychological related parameters, compared to the short term interventions. The mechanism that exercise can induce changes in the mental status of the patient is not fully understood, however, improvements in sleep [131], fatigue [132], functional capacity [133], and overall QoL [122] could at least partially explain the psychological improvement seen in those patients after the exercise training period. Aerobic exercise training exerts also acute benefits on the human brain by increasing the levels of an endogenous opioid called β-endorphin [134]. This is the reason of the euphoria sensation most of the patients get after the completion of an exercise session. That finding supports the hypothesis of endogenous opioid system involvement in the pathogenesis of the depression syndrome and a possible mechanism for explaining the exercise benefit observed in various exercise studies, however, further examination in the future is demanding.

Research Paper 1: Emotional intelligence in hemodialysis patients: The effect of an intradialytic exercise program.

Abstract

Introduction*:* It has been shown that patients receiving hemodialysis (HD) therapy experience very low levels of quality of life, that are usually accompanied by significant emotional distress symptoms such as depression and anxiety. Additionally it has been emphasized the important relation between emotional intelligent (EI) and health-related quality of life in patients with chronic diseases. Studies have shown that high levels of EI were negative related to anxiety symptoms and depression while sleep disturbances, fatigue and depression, which often seen in HD patients are associated with the level of EI in healthy subjects.

Aims: The purpose of this study was to investigate whether a relationship among emotional intelligence, functional capacity, fatigue, cognitive function and quality of life in patients on hemodialysis existed. Furthermore, this study aimed to assess the effect of a nine month intradialytic exercise training program on emotional intelligent status.

Methods*:* 78 dialysis patients under HD treatment (50M/28F, 60.6±17.2 years) were participated in the study. A subgroup of 18 patients (15M/3F, 56.7±12.3) completed a 9-month supervised intradialytic exercise training program (3 times weekly). Functional capacity assessed by a battery of tests (sit to stand), while emotional intelligent, sleep quality, depression levels and daily sleepiness status were assessed via validated questionnaires, before and after the intervention period. The 78 patients were divided into 2 groups, according to their assign scores in EI scales using both WLEIS and SSEIT scales.

Results*:* There were no significant correlations between patients' characteristics and EI score. However, there was a significant positive correlation among WLEIS score and physical health ($r= .191$, $p= .037$) and MVQOLI ($r = .255$, $p < .007$). WLEIS negatively associated with FSS ($r= -.215$, $p= .024$) and MFI ($r= -.206$, $p= .031$). SSEIT was positively associated with MMSE ($r= .268$, $p < .029$) and MSQOL ($r= .205$, $p < .027$). Also, SSEIT was negatively associated with FSS ($r= -.222$, $p= .018$) and MFI ($r= .255$, $p < .006$). After nine months of exercise training, group with low WLEIS score was significant increased compared to the baseline values (98.7±7.0 vs 73.0±4.0, $p= 0.020$) but no changes in the medium or high EI groups were observed.

Conclusion*:* Patients with higher levels of emotional intelligent showed increased levels of quality of life and lower levels of fatigue. Patients with low levels of emotional intelligent

are more likely to be benefited by an exercise training program compared to medium and high level counterparts.

Introduction

Patients with chronic kidney disease (CKD) at end-stage usually as a treatment receive hemodialysis (HD) therapy, which is considered as both a life-saving and life-altering process. The disease per se and especially the HD therapy induce serious alterations in patient's life and accordingly all these changes have a negative impact on their quality of life. Specifically, it has been demonstrated that patients receiving HD therapy experience very low levels of quality of life, that are usually accompanied by significant emotional distress symptoms such as depression and anxiety [135].

Additionally, it has been supported that low score of quality of life is strongly correlated with hospitalization and mortality and accordingly is considered as an established predictor of these two factors [136-138]. Furthermore, the low levels of quality of life that renal patients presents have found to be associated with the patient's mental, social and physical problems [67, 135]. Additionally, recently it has been supported that an association between low levels of quality of life and depressive symptoms in HD patients existed [69, 70, 139].

Recently it has been emphasized the important relation between emotional intelligent (EI) and health-related quality of life in patients with chronic diseases [140]. Specifically a study by Rey et al [140].who examined EI, personality and their relation to health-related quality of life in cancer patients, found that medical process and especially certain psychological resources influenced the health-related quality of life. The authors proposed that this variable could be a useful tool to assess and identify patients who may be at risk for experiencing low health-related quality of life [140].

EI refers to a set of social cognitive abilities specifically related to emotions. EI has been conceptualized as "the ability to engage in sophisticated information processing about one's own and others' emotions and the ability to use this information as a guide to thinking and behavior"[141].

It has been reported that high levels of EI were negative related to anxiety symptoms [142] and depression [143]. Moreover, sleep disturbances, fatigue and depression, which are common problems in patients on HD [57], have found to be associated with EI in healthy subjects [144]. Specifically, a study by Brown and Schutte, where the role of EI in fatigue of mature-aged and younger first-year psychology students examined [144], supported that higher EI score was associated with less fatigue. In addition, the relationship between EI and experienced emotions before successful and unsuccessful performance was studied in

student athletes and found that emotions which associated with successful performance were vigor, happiness, and calmness, whereas emotions associating with poor performance included confusion, depression and fatigue (Lane, Thelwell et al. 2009b).

However, at the literature there is limited information regarding EI levels on patients on HD. Only one study by Khan et al (1971) has examined the emotional status, level of intelligence, and self-concept in children with CKD and found that the highest percentage of the children suffered from serious social and emotional difficulties, such as feelings of social isolation, excessive dependency upon the parents, and depression [71]. Thus, as few studies have examined the relationship among EI, quality of life and other psychological variables in HD patients, the aim of this study was to investigate whether a relationship among emotional intelligence, functional capacity and quality of life in patients on hemodialysis existed and whether an exercise intervention training program could improve their levels.

Methods

Ethics Statement

The study was approved by the Human Research and Ethics Committee of the University of Thessaly, and by the bioethics committee of the University General Hospital of Larissa, and the General Hospital of Trikala, Greece. All patients gave their written informed consent prior to study participation.

Study Population

Seventy-eight dialysis patients (50M/28F, 61.2±17.1), were recruited from the local HD units. The 78 patients were divided into two groups, according to their assign scores in the Emotional Intelligent scales (EI) however, since two different scales of EI (WLEIS and SSEIT) have been used to assess EI levels in the current study, the 78 patients have been divided in two groups per scale as low WLEIS and high WLEIS as well as low SSEIT and high SSEIT. Therefore 4 patients' subgroups have been used using the quartiles approach. More specifically two low score groups of two EI scales (low WLEIS, low SSEIT) patients were stratified into quartiles: quartile I, <79, quartile II <110.75 respectively. Also two high score groups of two EI scales (high WLEIS, high SSEIT) patients were stratified into quartiles: quartile III, >96, quartile IV >134 respectively.

The 78 patients were also assessed for eligibility in order to participate in a 9 month exercise training program (Flow Chart). Eighteen stable HD patients (15M/3F, 56.7±12.3) completed the 9-month supervised exercise training program during HD (3 times weekly) which was supervised by 2 specialized exercise trainers. The eighteen patients were divided in 3 groups according to the WLEIS score into low, medium and high WLEIS score for further analysis (Table 7).

Inclusion & Exclusion criteria

Inclusion criteria were: dialysis for at least six months or more with adequate dialysis delivery (Kt/V > 1.1), and with Table clinical condition. Exclusion criteria were: patients unable to give informed consent, opportunistic infection in the last 3 months, malignancy or infection requiring intravenous antibiotics within 2 months prior to enrollment, with HIV, or musculoskeletal

contraindication to exercise or requirement for systemic anticoagulation, participating or having participated in an investigational drug or medical device study within 30 days or five half-lives, pregnant, breast feed or female of childbearing potential who did not agree to remain abstinent or to use an accepTable contraceptive regimen. Also, patients who were judged to have clinically significant abnormalities upon clinical examination or laboratory testing, or who were unable to adequately cooperate because of personal or family conditions, or those who suffered from a mental disorder that interferes with the diagnosis and/or with the conduct of the study, e.g. schizophrenia, major depression, dementia were excluded from this study.

HD procedure

The patients underwent the HD therapy (Fresenius 4008B, Oberursel, Germany) 3 times per week with low flux, hollow-fiber dialyzers and bicarbonate buffer. The HD session lasted 4 hours. An enoxaparin dose of 40-60 mg was administered intravenously before the beginning of each HD session. EPO therapy was given after the completion of HD session in order to normalize hemoglobin levels within 11-12 (g/dL).

General Study Design

Patients were assessed before (PRE) and after (POST) the 9-month aerobic exercise training program. Training was implemented during their HD session while the exercise program was supervised by 2 specialized exercise trainers. Cycle exercise was performed 3 times weekly for 60 minutes each time starting between the first 2hr of HD using an adapted cycle ergometer (Model 881 Monark Rehab Trainer, Varberg, Sweden) at an intensity of 50-60% of the patient's maximal exercise capacity, which was estimated during a previous HD session [145, 146]. During and before release from the HD unit, body mass, systolic and diastolic blood pressures (SBP, DBP) and heart rate (using the RS800CX, Polar Electro Oy, Kempele, Finland) were monitored and recorded. Participants' blood chemistry records were recorded before and at the end of the 9-month study. Participants were assessed in aspects related to mental and physical health as well as for exercise and functional capacity.

Exercise capacity

Using an incremental cycle ergometer test [146] exercise capacity was assessed before, at 3 months, at 6 months and at the end of the 9-month exercise intervention. Values recorded were used to re-adjust the submaximal training intensity of the intradialytic exercise sessions of this program.

Functional Capacity

The patient's functional ability levels were evaluated via a battery of functional tests: Two Sit-to-Stand tests from which three scores were recorded (time taken to complete 5 sit-to-stands STS-5, number of repetitions in 30'' STS-30 and number of repetitions in a whole minute, STS-60).

Handgrip strength

Maximum isometric handgrip strength, (HGS), was measured on the non-fistula (dominant) side [147] before, every hour during a dialysis session and 30 minutes after the end of HD using a handgrip dynamometer (Charder MG4800 Medical Handgrip Dynamometer, Charder Electronic Taiwan). The dynamometer was adjusted so that it fits comfortably to subjects palm size. Before data collection, a warm-up – familiarisation session was performed followed by 2 min rest. Subjects were instructed to grip the dynamometer and apply maximum force in response to a voice command. The subjects stood with both arms extended sideways from the body with the dynamometer facing away from the body. Two trials were performed with a rest period of at least 1 min between trials and the highest HGS value, before and after the HD session, was used in the analyses.

The patients' dry weight (ideal weight after removal of excess fluids) was recorded. Together with patients' height it was used to calculate body mass index (BMI). Waist and hip peripheries were measured and the waist to hip ratio (WHR) was calculated. Body composition was assessed using a whole-body, multi-frequency, bio-impedance spectroscopy system (BCM®, Fresenius Medical Care, Bad Homburg, Germany), to estimate fat mass (FM), lean tissue mass (LTM), total body

water (TBW) and body cell mass (BCM) [148]. The body composition measurements were taken immediately before the initiation and after the completion of the HD session and with the participants rested in the supine position. Electrodes were placed on the wrist of the arm without the arterio-venous fistula as well as on the ipsilateral ankle and connected to the BCM device [149].

Questionnaires

Fatigue

Fatigue was estimated using various questionnaires evaluating chronic and acute aspects of fatigue. General fatigue was assessed by Fatigue Severity Scale (FSS) [150]. This questionnaire contains nine statements concerning respondent's fatigue to measure fatigue severity. For subacute fatigue, we used the Brief Fatigue Inventory (BFI) [151] which is an instrument that can be administered in a clinical setting to assess the severity of fatigue experienced by patients, as well as its impact on their ability to function over the previous 24h. Finally, the Multidimensional Fatigue Inventory (MFI) [152], which is a 20-item scale designed to evaluate the dimensions of general fatigue, physical fatigue, reduced motivation, reduced activity, and mental fatigue was applied to the participants.

Cognitive function

Cognitive Function was assessed by the Mini Mental State Examination questionnaire (MMSE) [153], which is a brief 30-point questionnaire test and evaluates cognitive impairment. This questionnaire consists of simple questions and problems in a number of areas: the time and place of the test, repeating lists of words, arithmetic such as the serial sevens, language use and comprehension, and basic motor skills.

Symptoms of Depression

Depressive symptoms were evaluated using the Zung Self Rating Depression Scale (with a score > 44 being considered the cut-off for diagnosis of depression). Moreover, the Beck Depression Inventory II (Beck Depression Test, BDT) [154] was used to assess the intensity of depression.

Emotional Intelligence

Emotional intelligence was assessed by two tests. Firstly, the Schutte Self Report Emotional Intelligence Test (SSEIT) [155] was used. This instrument is a 33 item self-report where patients are asked to indicate their responses to items reflecting adaptive tendencies toward emotional intelligence according to a 5-point scale, with "1" representing strong agreement and "5" representing strong disagreement.

Secondly, Wong and Law Emotional Intelligence Scale (WLEIS) [156] which is a shorter instrument, was applied to the participants. This test contains 16 items grouped in four subscales as follows: (a) self-emotion appraisal (SEA), (b) emotion appraisal of others (OEA), (c) use of emotion (UOE), and (d) regulation of emotion (ROE).

Pain perception

Each subject was also asked to complete the Fibromyalgia Impact Questionnaire (FIQ) [157]. This self-administered questionnaire developed to measure fibromyalgia (FM) patient status, progress and outcomes. The instrument contains 11 questions measuring physical functioning, work status (missed days of work and job difficulty), depression, anxiety, morning tiredness, pain, stiffness, fatigue, and well-being over the past week.

Perceived Quality of Life

Quality of life was assessed by the Generic Medical Outcomes Survey 36 Item–Short Form (SF-36) [158] that contains eight dimensions, generating a profile of health-related quality of life. These dimensions are: 1) Physical Functioning; 2) Role Limitations due to Physical Functioning; 3) Bodily Pain; 4) General Health Perceptions; 5) Vitality; 6) Social Functioning; 7) Role Limitations due to Emotional Functioning; and 8) Mental Health. Total SF36 QoL score ranges from 0 (extremely poor) to 100 (very good). Moreover, the quality of life according to the clinical setting was evaluated by the Missoula-Vitas Quality of Life Index Version-15R. The MVQOLI is an assessment instrument that gathers patient - reported information about quality of life during advanced illness. We used the short version of 15-items questionnaire for dialysis patients [159].

Sleep and sleepiness

Sleep disturbances and usual sleep habits during the preceding month were evaluated by the Pittsburgh Sleep Quality Index (PSQI), which contains 19 questions [160].

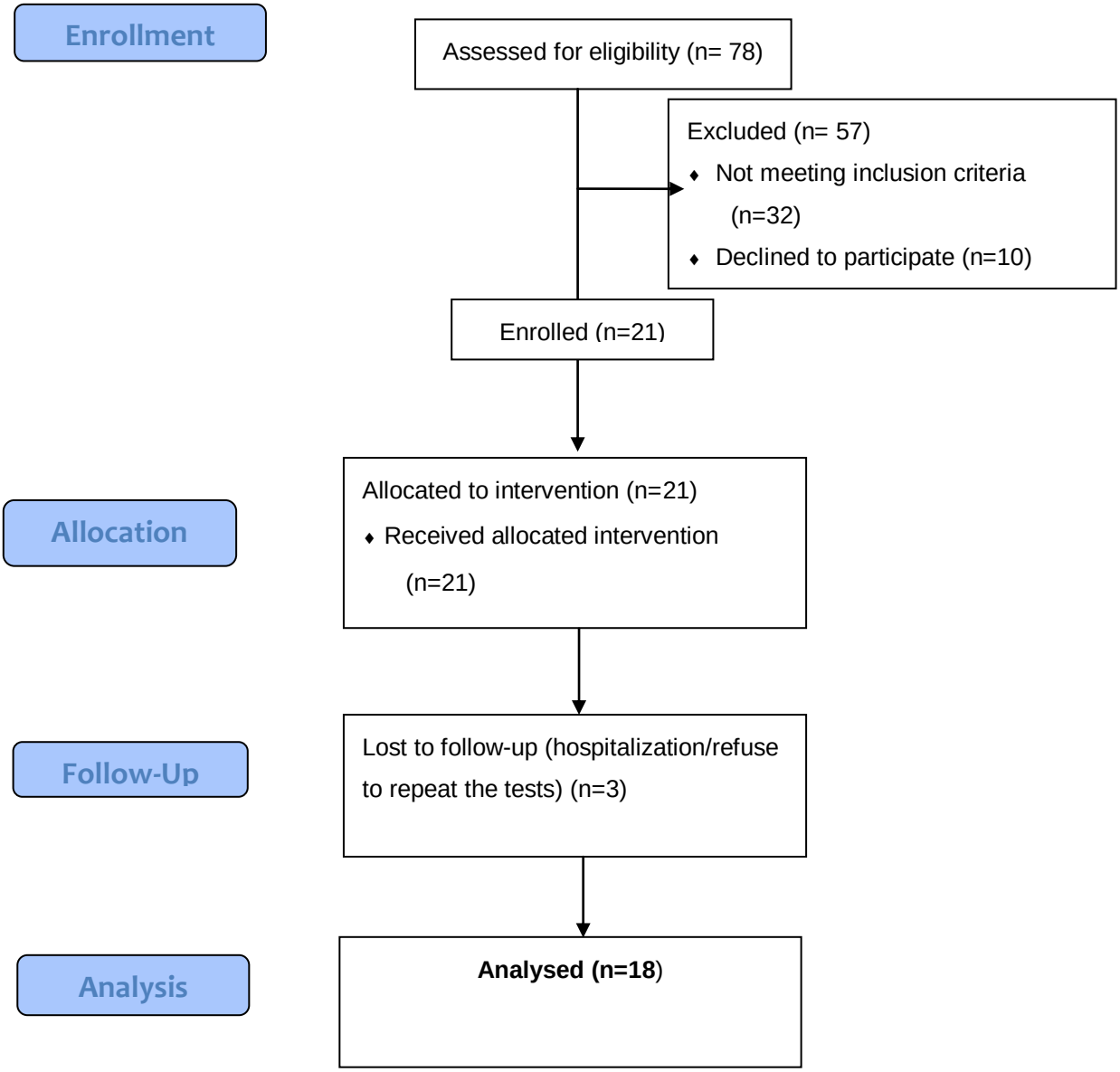
Furthermore, the HD patient's daily sleepiness status was assessed by the Epworth sleepiness scale (ESS) [161]. This scale differentiates between average sleepiness and excessive daytime sleepiness that requires intervention.

Statistical analysis

Continuous variables were analyzed using independent sample t-test. In case of outcome variables which changed in the same direction in both the progressive exercise and control groups, between-group comparisons were also made (comparing Δ-change values) to evaluate if the change in one group was significantly greater than that of the other group. Kendall's correlation test was used to assess the relationships between the examined variables. For comparing initial and final values (pre and post exercise training) were performed two-way repeated measures analysis of variance (ANOVA) All statistical analyses were performed using the SPSS version 18.0 (SPSS Inc. Chicago, Illinois). Data are presented as mean ± SD and the level for statistical significance was set at $p \leq 0.05$.

Results

Flow Chart



Data were analyzed from a total of 78 subjects who enrolled in the study. Table 1 shows the baseline characteristics of the participants. All the patients successfully completed the questionnaires and no adverse effects were reported. The mean age of the participants was 60.6±17.2 years old.

Table 1. Patient's basic characteristics, functional capacity and questionnaires assessment

Variables	**Pool Data**	**Pre Training Group**	**Post Training Group**	**P Value***
M/F	50/28	15/3	15/3	
Age	61.2±17.1	56.7±12.3	56.7±12.3	
BMI	25.8±4.9	25.4±4.4	25.9±4.7	0.080
WHR	1.0±0.1	1.0±0.1	1.0±0.1	0.914
pills/day	7.7±4.7	8.0±5.0	7.6±4.0	0.270
Kt/V	-	1.56±0.45	1.48±0.33	0.463
Months in dialysis	63.4±67.0	52.7±47.5	61.7±47.5	
MMSE	25.3±2.9	26.3±1.9	27.0±2.0	**0.010**
FSS	4.9±2.4	3.6±1.3	3.6±1.6	0.989
FIQ	22.5±16.1	14.9±4.6	7.4±5.7	**0.000**
WLEIS	86.2 ± 12.6	88.4±9.3	89.4±12.6	0.802
SSEIT	121.5 ± 19.9	128.8±12.7	133.2±16.3	0.438
SF36-Physical Health	75.9±89.6	65.9±17.8	66.9±18.1	0.760
SF36-Mental	66.4±66.6	65.0±11.1	65.0±12.3	0.955

Health				
SF36-TOTAL	48.7±21.5	70.0±13.1	67.0±15.8	0.418
BDI	9.5±7.4	5.3±4.9	6.9±6.4	0.195
MVQOL	16.1±4.3	18.3±3.6	18.7±3.2	0.664
ESS	4.5±2.6	4.3±2.6	5.4±2.8	0.328
PSQI	9.3±4.8	5.6±3.0	5.9±4.9	0.771
Pain	1.7±3.6	0.1±0.6	0.1±0.5	0.331
BFI	2.7±2.6	1.5±1.1	1.9±1.8	0.332
Handgrip Nw	23.5±10.8 (N=38)	26.5±8.2	29.4±8.2	**0.031**
STS 5(sec)	10.9±4.4 (N=24)	12.7±5.2	9.6±3.2	**0.042**
STS30(rep)	12.1±3.5 (N=24)	11.5±2.4	16.1±3.7	**0.001**
STS60(rep)	22.4±7.1 (N=24)	20.0±5.2	28.7±7.6	**0.001**
steps per week	44102.9±25875.1 (N=78)	52.583.7±26077	49507.1±32312.5	**0.286**

Abbreviations: BMI, Body Mass Index; WHR, Waist to Hip Ration; Kt/V, dialysis efficiency;MMSE, Mini Mental State Exam; FSS, Fatigue Severity Scale; FIQ, Fibromyalgia Impact Questionnaire; WLEIS, Wong and Law Emotional Intelligence Scale; SSEIT, Schutte Self-Report Emotional Intelligence Test; BDI; Beck Depression Inventory; MVQOLI, Missoula-VITAS Quality of Life Index; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; BFI, Brief Fatigue Inventory; STS, Sit to Stand.

** Pre Post comparisons*

The results of the correlations between patients' characteristics and functional capacity are presented in Table 2-4. At baseline, no significant correlations were observed between patients' characteristics and EI scores. However, a significant positive correlation between WLEIS scores and physical health ($r = .191$ $p < .037$) as well as between WLEIS and MVQOL ($r = .255$, $p < .007$).) was observed. In addition, WLEIS was negatively associated with FSS ($r = -.215$, $p < .024$) and MFI ($r = -.206$, $p < .031$). Moreover, the SSEIT results was positively associated with MMSE ($r = .268$, $p < .029$), and MVQOL ($r = .205$, $p < .027$) scores and negatively correlated with FSS ($r = -.222$, $p < .018023$) and MFI ($r = -.255$, $p < .006$) results.

Table 2. Patient's basic characteristics, functional capacity and questionnaires assessment

	Gender	Age	BMI	WHR	pills/day	months on dialysis	HandGrip
WLEIS	r=.037	r= -.710	r=-.094	r=.070	r=-.190	r= -.150	r=.091
	p=.740	p=.450	p=.350	p= .642	p=.098	p= .195	p=.443
SSEIT	r=-.062	r=-.117	r=-.007	r=.006	r=.023	r=.037	r=.070
	p=.569	p=.209	p=.942	p=.966	p=.839	p=.745	p=.551

Abbreviations: BMI, Body Mass Index; WHR, Waist to Hip Ration; ABI, Ankle Brachial Index.

Table 3. Correlations between patients' emotional intelligence tests and questionnaires

	MMSE	FSS	FIQ	Physical Health	Mental Health	WLEIS	SSEIT
WLEIS	r=.216	r=-.215(*)	r=-.023	r=.191(*)	r=.064		r=.407**
	p=.081	p=.024	p=.848	p=.037	p=.488		p=.000
SSEIT	r=.268(*)	r=-.222(*)	r=.146	r=.058	r=.050	r=.407**	
	p=.029	p=.018	p=.218	p=.524	p=.579	p=.000	

Abbreviations: MMSE, Mini Mental State Exam; FSS, Fatigue Severity Scale; FIQ, Fibromyalgia Impact Questionnaire; WLEIS, Wong and Law Emotional Intelligence Scale; SSEIT, Schutte Self-Report Emotional Intelligence Test. $* p<0.05$, $** p<0.01$.*

Table 4. Correlations between patients' emotional intelligence tests and questionnaires (continue)

	BDI	MVQOLI	ESS	PSQI	PAIN	MFI	BFI
WLEIS	r=-.109	r=.255**	r=.002	r=-.077	r=.104	r=-.206*	r=-.195
	p=.254	p=.007	p=.985	p=.440	p=.421	p=.031	p=.102
SSEIT	r=-.140	r=.205*	r=-.054	r=-.001	r=.145	r=-.255**	r=-.031
	p=.139	p=.027	p=.576	p=.995	p=.256	p=.006	p=.796

*Abbreviations: BDI; Beck Depression Inventory; MVQOLI, Missoula-VITAS Quality of Life Index; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; MFI, Multidimensional Fatigue Inventory; BFI; Brief Fatigue Inventory. * $p<0.05$, ** $p<0.01$.*

A t-test was conducted in order to determine if significant differences in EI scores between divided groups existed: low WLEIS, low SSEIT, high WLEIS, and high SSEIT. The EI data are presented in Table 5. There were no significant differences between the groups in functional capacity tests performed. It was also observed, that MMSE score was higher in the high WLEIS group [M (high EI WLEIS) =26.7, SD = 1.5, p=.011] than low WLEIS group [M (low EI WLEIS) = 25.0, SD = 3.1, p=.011]. Also, scores of quality of life (MVQOL) had significant differences between WLEIS group patients, namely higher quality of life corresponded to high WLEIS scores [M (high EI WLEIS) = 18.6, SD = 3.8, p= .013)] and poor quality of life represented lower WLEIS scores [M (low EI WLEIS) = 15.6, SD = 4.1, p= .013].

There was a statistically significant difference between the general perceptions of fatigue scores (FSS, BFI) and divided groups of EI regarding the WLEIS scores (Table 5). Furthermore, it was observed that patients with lower EI score showed higher score in general fatigue. Specifically, FSS score was higher in the low WLEIS group [M (low EI WLEIS) = 5.2, SD = 2.5, p=.044] than in the group with high WLEIS score [M (high EI WLEIS) = 3.9, SD = 1.9, p=.044]. BFI score was correspondingly high in the low WLEIS group [M (low EI WLEIS) = 3.0, SD = 2.7, p=.011] than in the WLEIS group [M (high EI WLEIS) = 1.4, SD = 1.3, p=.011].

Taking into account the differences in the questionnaires score regarding the EI status in the HD patient's groups, MMSE score observed increased in the group with high score in the SSEIT [M (high EI SSEIT) =26.8, SD = 2.5, p=.046] while the group with low SSEIT score had low score at the MMSE [M (low EI SSEIT) = 25.0, SD = 2.9, p=.046]. In addition, there was a statistically significant difference between the general perceptions of fatigue scores (FSS, MFI) and divided groups of EI (Table 5). Patients with low EI status showed higher scores in the general fatigue. Specifically, FSS score was higher in the group with low SSEIT score [M (low EI SSEIT) = 5.1, SD = 2.6, p=.015] than in the group with high SSEIT score [M (high EI SSEIT) = 3.9, SD = 1.8, p=.015]. Furthermore, MFI score still was correspondingly high in the low SSEIT group [M (low EI SSEIT) = 61.9, SD = 19.1, p=.008] than high SSEIT group [M (high EI SSEIT) = 47.9, SD = 16.6, p=.008].

Table 5. Basic characteristics, functional capacity and questionnaires data divided in two groups according to scores in the two Emotional Intelligence questionnaires

Variables	Low EI SSEIT	High EI SSEIT	Low EI WLEIS	High EI WLEIS	P value
N	54	16	58	17	
Gender (M/F)	37/17	10/6	41/17	9/8	0.672
					0.213
Age	61.3±17.9	56.9±15.1	62.3±16.8	56.7±17.9	0.337
					0.259
BMI	26.8±4.9	24.1±4.7	26.3±5.1	24.4±4.2	0.069
					0.125
WHR	1.0±0.1	1.0±0.4	0.9±0.1	1.0±0.3	0.648
					0.409
ABI	1.0±0.1	1.0±0.2	1.0±0.1	1.0±0.1	0.765
					0.337
Months in	69.4±76.4	53.6±37.9	72.1±73.7	45.3±45.9	0.338

Dialysis					0.125
Hand Grip (Newton)	23.7±11.1	26.4±10.4	23.8±11.0	26.1±10.6	0.461 0.493
Questionnaires					
WLEIS	84.4±13.2	93.4±8.4	82.3±11.7	99.4±2.8	**0.003 **** **0.000****
SSEIT	114.7±17.3	143.9±6.8	117.8±20.5	133.6±10.9	**0.000**** **0.000****
MMSE	25.0±2.9	26.8±2.5	25.0±3.1	26.7±1.5	**0.046 *** **0.011 ***
FSS	5.1±2.6	3.9±1.8	5.2±2.5	3.9±1.9	**0.045 *** **0.044 ***
MFI	61.9±19.1	47.9±16.6	60.8±19.0	51.7±18.6	**0.008 **** 0.095
BFI	2.6±2.6	2.5±2.6	3.0±2.7	1.4±1.3	0.912 **0.011 ***
Physical Health (SF36)	82.0±93.4	55.9±36.8	66.9±80.8	96.7±85.6	0.100 0.213
Mental Health (SF36)	69.4±74.3	65.4±49.5	70.7±74.9	55.3±24.7	0.805 0.185
MVQOL	16.0±4.2	17.8±4.3	15.6±4.1	18.6±3.8	0.144 **0.013***
BDI	9.9±7.5	7.3±7.1	9.8±7.4	7.4±6.7	0.221 0.226
ESS	4.5±2.5	4.3±3.0	4.2±2.5	4.9±2.9	0.839 0.437
PSQI	8.5±5.3	8.6±4.7	8.5±5.0	8.2±5.5	0.940

					0.865
FIQ	22.4±15.7	25.2±18.0	24.1±16.9	19.6±13.3	0.653
					0.341
PAIN	1.6±3.5	2.4±3.4	1.6±3.5	2.1±4.0	0.512
					0.658

Abbreviations: BMI, Body Mass Index; WHR, Waist to Hip Ration; ABI, Ankle Brachial Index; WLEIS, Wong and Law Emotional. Intelligence Scale; SSEIT, Schutte Self-Report Emotional Intelligence Test; MMSE, Mini Mental State Exam; FSS, Fatigue Severity Scale; MFI, Multidimensional Fatigue Inventory; BFI; Brief Fatigue Inventory; MVQOLI, Missoula-VITAS Quality of Life Index; FIQ, Fibromyalgia Impact Questionnaire; BDI; Beck Depression Inventory; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; FIQ, Fibromyalgia Impact Questionnaire. . $p<0.05$, ** $p<0.01$.*

The subset of 18 patients completed the exercise intervention. Their mean age was 56.7±12.3 years (15 males) and their mean duration in HD treatment was 61.7±47.5 months. There were no significant differences between pre and post exercise training in sum scores of WLEIS (88.4±9.3 vs 89.4±3.0, p=0.802) and SSEIT (128.8±12.7 vs 133.2±16.3, p=0.438) (Table 6).

Table 6. Effect of 9 months exercise training on the Emotional Intelligence questionnaires

	Pre Training	**Post Training**	**p values**
N	18	18	
WLEIS	88.4±9.3	89.4±3.0	0.802
SSEIT	128.8±133.2	133.2±16.3	0.438

Abbreviations: WLEIS, Wong And Law Emotional Intelligence Scale; SSEIT, Schutte Self-Report Emotional Intelligence Test

Two-way repeated measures analysis of variance (ANOVA) were conducted to determine if there were significant differences in WLEIS EI test between divided groups: low WLEIS, medium

WLEIS, high WLEIS. The EI data are presented in Table 7. Low WLEIS has significant difference post exercise training compare to the baseline value (73.0±4.0, p= 0.020).

Table 7. Effect of 9 months exercise training on the Emotional Intelligence questionnaire WLEIS. Data divided in three groups according to scores in the Emotional Intelligence test

	Low	**Medium**	**High**	**p values**
N	3	11	4	
Pre WLEIS score	73.0±4.0	88.6±4.7	99.2±2.6	**0.020**
Post WLEIS score	98.7±7.0*	85.7±14.0	92.5±7.9	0.541
Delta changes	25.7±6.4	-2.9±15.2	-6.7±5.9	0.106

*Abbreviations: WLEIS, Wong and Law Emotional Intelligence Scale * Pre Post differences, ** Between groups*

No correlation was observed between functional and emotional intelligence indices (Table 8).

Table 8. Correlations between patients' emotional intelligence and functional ability after the 9 months training

	STS5(sec)	**STS30(rep)**	**STS60(rep)**
WLEIS	r=.032	r=.108	r=.098
	p=.845	p=.528	p=.556
SSEIT	r=-.048	r=.285	r=.290
	p=.77	p=.096	p=082

Abbreviations:WLEIS, Wong and Law emotional intelligence scale; SSEIT, Schutte Self-Report Emotional Intelligence Test; STS; Sit-To-Stand,

In addition, after 9 month of exercise training, no relations between emotional intelligence and body composition indices were found (Table 9).

Table 9. Correlations between patients' emotional intelligence tests and body composition indices

	Total Fat (kg)	**TBW (L)**	**LTM (kg)**	**BCM (kg)**
WLEIS	r=-.165	r=.088	r=.077	r=.088
	p=.412	p=.661	p=.702	p=.661
SSEIT	r=-.067	r=-.157	r=.045	r=.056
	p=.741	p=.440	p=.826	p=.783

Abbreviations:WLEIS, Wong And Law Emotional Intelligence Scale; SSEIT, Schutte Self-Report Emotional Intelligence Test; TBW, Total Body Water; LTM; Lean Tissue Mass; BCM, Body Cell Mass.

Discussion

This study investigated whether a relationship between EI, functional capacity, cognitive function, fatigue and quality of life in HD patients existed and whether an exercise training program could change the level of EI in patients receiving HD therapy. The results of this study revealed that a significant correlation among EI and quality of life, fatigue and cognitive function in HD patients existed. However, nine months of exercise training during HD therapy were not enough to induce changes in EI status in these patients.

The relation between EI status and quality of life has been investigated in other patients with chronic diseases. Specifically, similar results have been reported by Yalcin et al who examined the effect of an EI program on the health-related quality of life and well-being in patients with type 2 diabetes. The authors found that a 12-week EI program had a positive impact on participants' quality of life, wellbeing, and EI status [162]. Moreover, in another study by Rey et al, who examined the relationship between EI and health-related quality of life in patients with cancer, found that EI predicted different health-related quality of life dimensions. The results of this study revealed a psycho-educational approach of EI, which could preserve or improve health-related quality of life of cancer patients [140]. More recently, a study by Benzo et al [163], who examined the association between EI status and quality of life in Chronic Obstructive Pulmonary Disease (COPD), confirmed the EI beneficial impact on patients quality of life. According to these authors EI is an ability, which can be learned, and could be a complementary, non-expensive tool to the rehabilitations programs aiming to improve the low levels of quality of life that patients with chronic diseases experience.

Furthermore, an association between EI and fatigue in HD patients was found in this study. Studies have shown that higher EI status was associated with less fatigue in healthy subjects [164]. Specifically, Brown and Schutte who assessed EI status in university students in combination with the psychosocial variables of depression, anxiety, optimism, internal health locus of control, amount of social support, and satisfaction with social support, indicated that EI and fatigue had an impact on each variable [164] . Indeed, previous studies which examined the relationship between EI and depression, revealed that a significant negative relationship between EI and depression exist [165]. Specifically, Downey et partners (2008) who investigated whether an association between EI and depression's clinical diagnosis existed, demonstrated that measurement of EI has a predictive

value for assessing patients with high risk for developing depression [165]. Furthermore, the negative relationship between EI and depression has been observed and among adolescents [166]. Specifically, a recent study by Balluerka et al demonstrated that high levels of emotional clarity and repair were related to lower levels of depressed mood in adolescents [167]. In addition, another study by Vlachaki et al (2013), who examined the relationship between different dimensions of EI and coronary heart disease, found that facets of trait EI were associated with high incidence of coronary heart disease [168].

A correlation between EI and cognitive function was found in this study, indicating that patients with higher EI score, revealed higher score in MMSE. Previous findings from other studies have supported that people with higher EI are most likely to perform higher score on a cognitive task [169] Moreover, individuals who confronted with difficulties in a cognitive task, they were able to ward off the detrimental emotional effects of difficulties and persist on the task [169].

However, nine months of exercise training were not enough to improve the EI status of the HD patients. These results could be attributed to the fact that the exercise intensity was low, between 50-60% of the patient's maximal exercise capacity. Regarding the association between EI and physical activity, a contemporary review by Grigoriou et al (2012), demonstrated that EI is positively related with good health and exercise habits. Most specifically participation in vigorous and moderate physical activities seems to have a positive effect on EI [170]. Solansky and Lane (2010) have supported that exercise beneficially regulates mood and this mood improvement had a positive impact on EI status. These authors suggested that exercise training could improve mood and accordingly increase EI scores [171]. EI could be developed and learned at any time or age and in combination with exercise training programs could increase wellbeing and better emotional regulation in patients with chronic diseases [163].

Conclusions

The results of this study indicated that EI could be considered as a valuable tool for the determination of the high risk for hospitalization and mortality patients. In summary, less of fatigue may be an indicator of high EI patients. Some psychological variables showed a negatively association with high EI score in HD patients and also help predict patients with high levels of quality of life. A better understanding of the interactions between factors that influence EI and functional capacity may help researchers to develop interventions for the quality of life improvement among dialysis patients.

Even though the EI is a construct that has not been recognized yet as a useful tool in healthcare, future research is needed to focus on healthcare aspects [172]. EI as a multi-dimensional construct could have an important role in public health enhancing the relationship between clinician-patient with little or no communication gap [173], with patients feeling empowered, knowledgeable, and it control of their health [174, 175] and feeling treated holistically in superior quality of healthcare [176, 177].

This is the first study which examined the association of end stage renal disease and EI, and evaluated the effect of exercise training program on EI patients'. Although we did not found any significant change of EI in this population further research is needed to estimate the beneficial effects of long term exercise training programs on emotional status in other clinical populations and focus on the implications of EI in the clinical domain.

Research Paper 2: A Single Bout of Intradialytic Exercise and its effects on Myocardial Stunning

Abstract

Introduction: Chronic kidney disease is a "silent epidemic" affecting up to 10% of the EU population. Cardiovascular diseases are the main cause of mortality in end-stage renal disease (ESRD) patients, especially those receiving hemodialysis (HD) therapy. One side effect of HD is recurrent myocardial ischemia and global or segmental left-ventricular dysfunction known as myocardial stunning which is associated with intradialytic hypotension, long-term loss of systolic function, and high incidence of cardiovascular events and death. Exercise training has beneficial effect for cardiovascular fitness and reducing mortality in ESRD. Whether there is an acute benefit of exercise during HD on a reduction in myocardial stunning is not known.

Aims: The aim of the current study was to investigate whether a single bout of intradialytic exercise could attenuate myocardial stunning observed during HD session.

Methodology: Twenty one stable HD patients participated in the study. All participants completed two different HD trials on two different days, separated by one week: (1) normal HD and, (2) HD including a single bout of intradialytic exercise. Echocardiographic assessment of ejection fraction was completed before HD, half an hour before the end of HD and 30 min after the end of HD. Echocardiographic scans were performed using an iE33 echocardiographic system. All images were acquired with the subject lying in the left lateral decubitus position with a 2.5 MHz transducer. Myocardial stunning was assumed when a >20% reduction in ejection fraction was observed. Generalized linear model (GLM) repeated measures were used to compare the 2 trial days.

Results: Cohort data for ejection fraction were not different between trials and did not change across time in either the HD or HD plus exercise trial. Cohort data for the change in ejection fraction from baseline to during HD did mask considerable inter-individual variability (HD - 0±15; HD plus exercise (-2±20). Despite this the variability was not mediated by the addition of intradialytic exercise.

Conclusions: A single bout of intradialytic exercise did not attenuate or augment myocardial stunning often seen at the end of HD. It is important to determine whether chronic exercise training could attenuate the severity of myocardial stunning often observed in HD patients.

Introduction

It is well known that undergoing HD patients show a strong risk of cardiovascular disease [87]. Cardiovascular events are a common cause of mortality in these patients [79].. Diabetes, hypertension, prolonged anemia arterial calcification and electrolyte imbalance are some factors that could predispose to cardiovascular mortality in patients undergoing HD [81].

In a study performed by McIntyre and colleagues divided the pathogenesis of Heart Failure (HF) in these patients. Intradialytic myocardial stunning (ischemia-mediated temporary reduction in cardiac function) may over time lead to irreversible fibrotic changes and chronic HF, arrhythmias, and sudden cardiac death (SCD) [178].

Also, pediatric study reported that even children who receive HD experience dialysis-induced myocardial stunning [179]. That means that the majority of undergoing HD patients show significant cardiac dysfunction regardless of age and cardiovascular risk profile [180]. Numerous studies enhanced the many beneficial effects of exercise in HD patients. Specifically exercise during HD sessions has improved some indicators of cardiac and SCD [181] and seems to enhance muscle wasting, self-reported physical function [65, 182, 183]. Still dialysis efficacy (measured by KT/V) and QOL have shown improvement[184]. It's important to clarify the importance of sustaining exercise program during in dialysis routine care resulting in improvement of psychological and physical sides effects in this population[185]. Whether there is an acute benefit of exercise during HD on a reduction in myocardial stunning is not known. The aim of the current study was to investigate whether a single bout of intradialytic exercise could attenuate myocardial stunning observed during HD session.

Methodology

Ethics Statement

The study was approved by the Human Research and Ethics Committee of the University of Thessaly, and by the bioethics committee of the University General Hospital of Larissa, and the General Hospital of Trikala, Greece. All patients gave their written informed consent prior to study participation.

Study population

Seventy eight patients were assessed for eligibility while only twenty one HD patients (17M/4F, 56±19years) participated in the study (Flow Chart). Patients were recruited from the HD unit of the local hospitals and all testing was performed on site in the hospital.

Inclusion & Exclusion criteria

Inclusion criteria were: dialysis for at least six months or more with adequate dialysis delivery (Kt/V > 1.1), and with stable clinical condition. Exclusion criteria were: patients unable to give informed consent, opportunistic infection in the last 3 months, malignancy or infection requiring intravenous antibiotics within 2 months prior to enrollment, with HIV, or musculoskeletal contraindication to exercise or requirement for systemic anticoagulation, participating or having participated in an investigational drug or medical device study within 30 days or five half-lives, pregnant, breast feed or female of childbearing potential who did not agree to remain abstinent or to use an acceptable contraceptive regimen. Also, patients who were judged to have clinically significant abnormalities upon clinical examination or laboratory testing, or who were unable to adequately cooperate because of personal or family conditions, or those who suffered from a mental disorder that interferes with the diagnosis and/or with the conduct of the study, e.g. schizophrenia, major depression, dementia were excluded from this study.

Study Design

Patients were assessed under two different scenarios taking place one week apart on the same day of dialysis (2^{nd} dialysis session): Scenario 1: normal HD and Scenario 2: HD including a single bout of

intradialytic exercise. The order of the two scenarios was randomly applied in all patients. In scenario, cycle exercise was performed between the first and second hour of the dialysis using an adapted bicycle ergometer (Model 881 Monark Rehab Trainer, Varberg, Sweden) at an intensity of 50-60% of the patient's maximal exercise capacity (W), which was estimated during a previous HD session [145].

HD procedure

The patients underwent the HD therapy (Fresenius 4008B, Oberursel, Germany) 3 times/week with low flux, hollow-fiber dialysers and bicarbonate buffer. The HD session lasting approximately 4 hours. An enoxaparin dose of 40-60 mg was administered intravenously before the beginning of each HD session. EPO therapy was given after the completion of HD session in order to normalize hemoglobin levels within 11-12 (g/dL).

Protocols: Body composition

Body composition was measured by a whole-body multi-frequency bio-impedance spectroscopy system (BCM®, Fresenius Medical Care, Bad Homburg, Germany). This estimates fat mass (FM), lean tissue mass (LTM), total body water (TBW) and body cell mass (BCM) [148]. The body composition measurement were taken immediately before HD session while the participants were rested in the supine position. Electrodes were placed on the wrist of the arm without the arterio-venous fistula and on the ipsilateral ankle and connected to the BCM device [149].

Echocardiography

Echocardiographic scans were performed using an iE33 echocardiographic system (Philips Medical Systems, Andover, MA, USA). All image acquisitions were made with the subject lying in the left lateral decubitus position using a 2.5 MHz transducer. For each patient, ≥ 3 consecutive beats were analyzed in each scan, and the mean value was used in the subsequent statistical analysis. All echocardiograms were performed by the same experienced echocardiographer. For the recording of HR, a single lead ECG inherent to the echocardiographic system was used. Left ventricular dimensions were determined from 2-dimensional guided M-Mode images according to the recommendations of the American Society of Echocardiography (ASE) for chamber quantification, [186] using the parasternal long-axis acoustic

window. LV mass was calculated from M-Mode traces at the level of mitral valve and determined in g by using the recommended ASE formula. LV mass index was calculated by dividing LV mass by body surface area (using the DuBois and DuBois formula) and height [187] to minimize effects of age, gender, and overweight status [186]. For the assessment of LV diastolic function, the transducer was applied apically (4-chamber view) whilst a pulsed wave Doppler sample volume (4 mm) was located at the tips of the mitral valve leaflets. Doppler gain, pulse repetition frequency, and high-pass filter were all adjusted in order to maximize the signal to noise ratio. The following parameters were evaluated: early peak flow velocity (E), late peak flow velocity (A); thus the ratio of E to A was calculated. The primary outcome variable was ejection fraction (EF) and change in ejection fraction (ΔEF) from baseline to intervention. Ejection fraction was calculated using the biplane Simpson's method from 2-dimensional apical 2- and 4- chamber orientation to evaluate the patient's systolic function. Myocardial stunning was assumed when a >20% reduction in ΔEF was observed. Tissue Doppler velocities were assessed at the basal septum, using pulsed-wave tissue Doppler imaging. The sample volume (2 mm) was placed at the basal septum at the level of the mitral annulus ring in parallel to the longitudinal movement of the septum. The high-pass filter was bypassed, and gains were set to a minimal value to obtain the best signal to noise ratio. Peak systolic (S') as well as early diastolic (E') and peak late diastolic (A') myocardial tissue velocities were assessed and the E'/A' ratio was calculated. In addition, the conventional Doppler E to tissue Doppler E' ratio (E/E') was calculated.

Blood Chemistry

Routine monthly laboratory results were recorded including c reactive protein, ferritin, iron, hematocrit, and hemoglobin. The analyses were performed at the clinical biochemistry lab of the University Hospital of Larissa under standard hospital procedures.

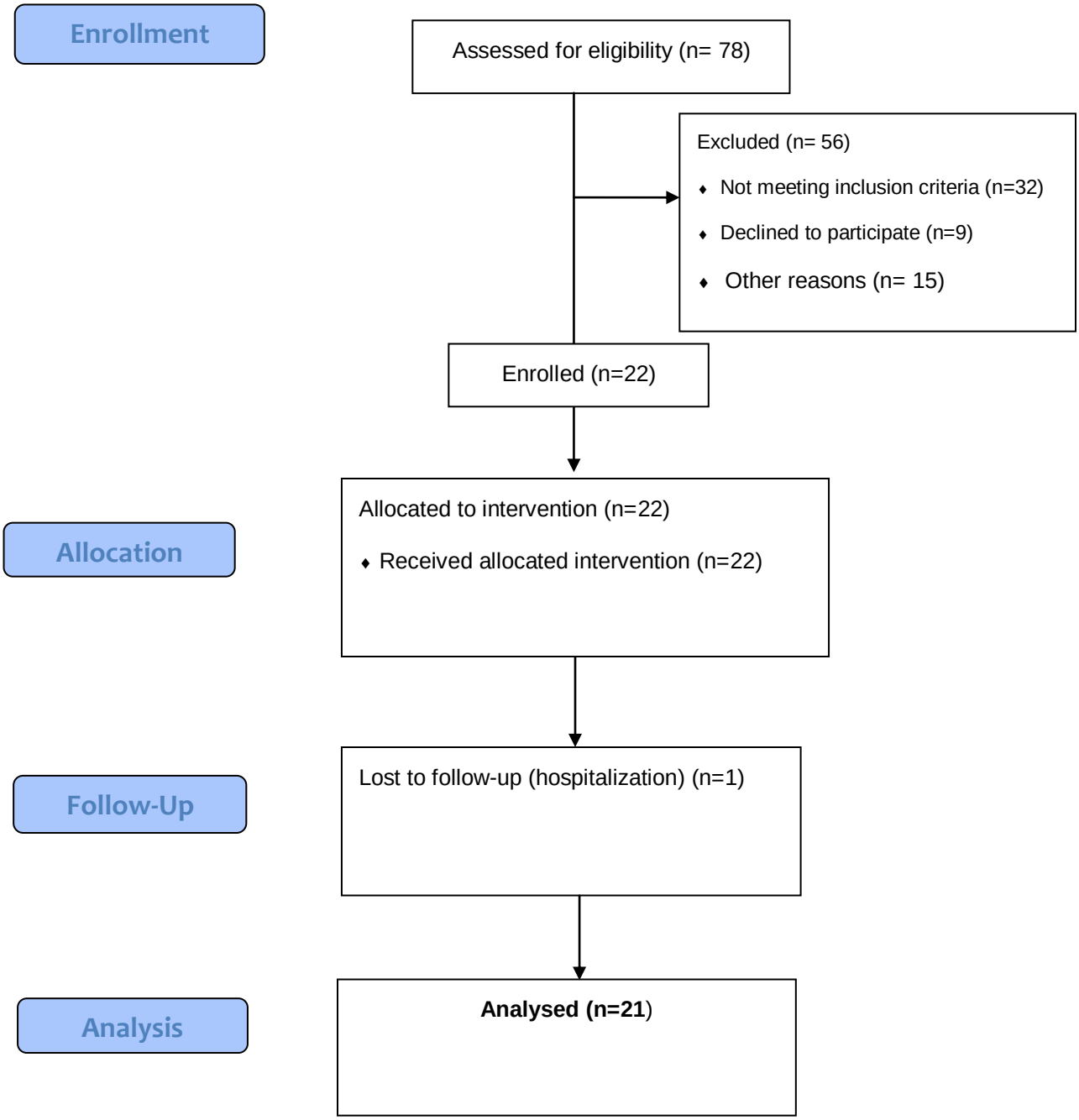
Statistical analysis

The results are expressed as mean ± SD. Statistical analysis was performed using two-way repeated measures analysis of variance (ANOVA). The Pearson product-moment correlation was used to assess the relationship between the body composition and echocardiographic indices. All the statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS for Windows, version 18.0,

Chicago III). Differences were considered significant when $P \leq 0.05$.

Results

Flow Chart



Patient basic characteristics are presented in Table 1. All twenty one stable hemodialysis patients who participated in the study completed both scenarios without any adverse effects.

Table 1. Hemodialysis patient basic characteristics

Variables	Values
N	21
Female/Male	4/17
Age (yr)	56±19
Weight (kg)	77.8±18.5
Height (m)	1.69±0.10
BMI (kg/m^2)	27.1±6.2
WHR	1.02±0.12
Steps per week	48250.6±26371.2
Months in dialysis	40±44
Kt/V	1.48±0.30
CRP(mg/dL)	3.2±4.2
HCT	34.8±3.8
Hb(g/dL)	11.3±1.2
Iron(μg/dL)	65.3±48.5
Ferritin (ng/mL)	1121.2±942.7
TBW (L)	35.1±7.2 /
Total Fat (kg)*	23.7±12.8
LTM (kg)*	42.3±10.4
BCM (kg)*	24.0 ±7.0

All data are mean ± SD. BMI, body mass index; WHR, waist to hip ratio; Kt/V, dialysis efficiency; CRP, C Reactive Protein; HCT, hematocrit; Hb, hemoglobin; TBW, total body water; LTM, Lean Tissue Mass; BCM, Body cell mass

Echocardiographic indices of LV structure at baseline between the two different scenario days are presented in Table 2. No differences were observed for any variable at baseline before the initiation of dialysis between the two scenario days.

Table 3. Echocardiographic indices of LV structure at baseline between the two different trial days

Parameter	**Scenario**	**Values**	**p value**
IVSTd (mm)	No Exercise	12 ± 2	0.443
	Exercice	11 ± 2	
LVPWTd (mm)	No Exercice	11 ± 2	0.952
	Exercice	12 ± 3	
LVmass (g)	No Exercise	57 ± 9	0.283
	Exercise	55± 15	
LVmass/BSA (g/m^2)	No Exercise	31 ±4	0.289
	Exercise	29 ± 8	
LVmass/height(g/m$^{[2.7]}$)	No Exercise	14 ± 4	0.277
	Exercise	14 ± 4	

All data are mean ± SD. IVSTd, interventricular septum thickness in diastole; LVPWTd, left ventricular posterior wall thickness in diastole; LV, left ventricle; BSA, body surface area.

LV loading and functional data across both trials are presented in Table 3. Pre-dialysis LVIDd values were not different between the two trials. There was a significant main effect for time as LVIDd was reduced by c.2-3 mm in both trials during dialysis with a return to baseline during recovery EF did not change across both trials (Table 2, Figure 1). Similarly the change in EF from baseline to peak dialysis was not different from zero although some individual variability was noted. (Table 2, Figure 2). Of the systolic functional variables only S' presented with a significant main effect for time (with an increase during dialysis and recovery in both trials compared to baseline).

Indices of diastolic function are also presented in Table 3. There was a significant main effect of time for E, A and A'. Data for E were reduced during dialysis compared to baseline in both trials with only a

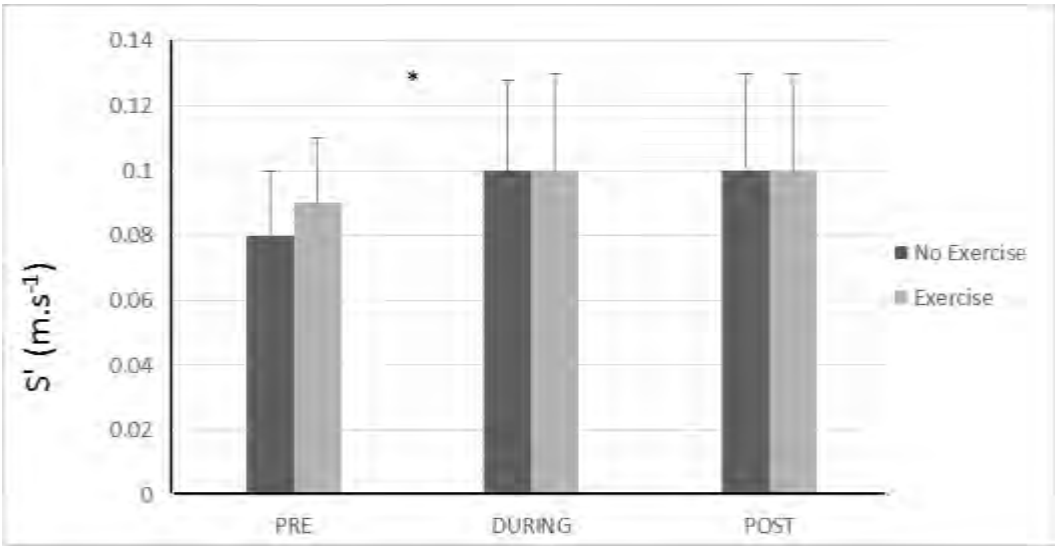
partial return recovery at the post-dialysis assessment. The same pattern was observed for A with absolute changes slightly smaller. Data for A' increased slightly at post assessment when compared to baseline and during dialysis time-points. All other variables did not change across either time point.

Table 2. Echocardiographic data for loading, systolic and diastolic function at baseline, during and post dialysis in the two scenario.

Parameter	**Scenario**	**Baseline**	**During**	**Post**
Preload				
LVIDd (mm)	No Exercise	47±6	45±6	46±5
	Exercise	46±6	43±5	45±5
Systolic Function				
EF (%)	No Exercise	51 ± 8	54±8	50±10
	Exercise	50 ± 12	53±9	49±13
Δ EF (peak	No Exercise		2.26 ± 9.5	
dialytic stress)	Exercise		5.74 ± 13.18	
S' (m/s)	No Exercise	0.08±0.01	0.11±0.02*[a]	**0.11±0.02**[†a]
	Exercise	0.09±0.02	0.11±0.02	0.11±0.02
Diastolic Function				
E (m/s) *	No Exercise	0.87±0.26	0.62±0.13	0.70±0.16
	Exercice	0.88±0.18	0.64±0.11	0.73±0.12
A (m/s) *	No Exercice	0.92±0.37	0.82±0.35	0.84±0.34
	Exercice	0.93±0.31	0.78±0.32	0.80±0.32
E/A	No Exercice	1.00±0.34	0.85±0.32	0.94±0.38
	Exercice	0.97±0.19	0.93±0.29	1.04±0.41
E' (m/s)	No Exercise	0.09±0.02	0.08±0.02	0.09±0.03
	Exercise	0.09±0.02	0.09±0.03	0.08±0.03
A'(m/s) *	No Exercise	0.09±0.02	0.08±0.02	0.09±0.02
	Exercise	0.09±0.02	0.09±0.02	0.10±0.02
E'/A'	No Exercise	1.12±0.50	1.03±0.48	1.06±0.54
	Exercice	1.01±0.40	1.04±0.46	0.84±0.40
E/E'	No Exercice	10±5	9±5	8±3
	Exercice	11±5	8±3	10±5

All data are mean ± SD. Δ , delta, EF, ejection fraction, S', annular systolic tissue velocity, E, transmitral doppler early diastolic wave; A, transmitral doppler atrial diastolic wave; E/A, ratio of E and A wave peak velocities; E', annular early diastolic myocardial velocity; A', annular late diastolic myocardial

*velocity; E'/A', ratio of early to atrial diastolic myocardial velocity; E/E', ratio of transmitral blood flow velocity to tissue doppler velocity. *Significant main effect of time*



** Significant main effect of time.*

Fig. 1. Ejection Fraction (EF%) at baseline, during and post dialysis with and without the implemented exercise session.

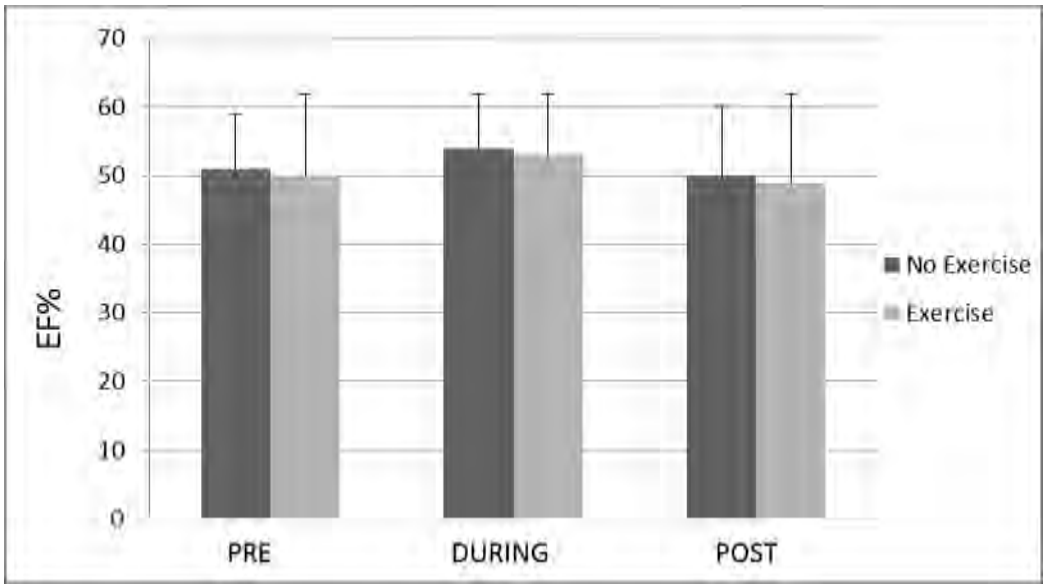
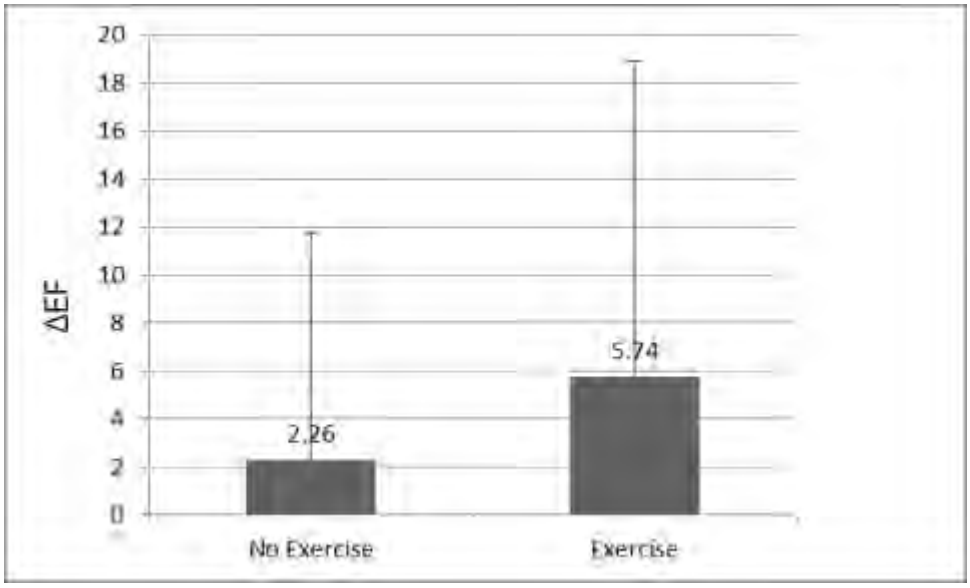


Fig. 2. ΔF (peak dialytic stress) during dialysis with and without the implemented exercise session.



Discussion

In this study we attempted to investigate the effect of acute exercise on myocardial stunning in hemodialysis patients. There is evidence showing that heart failure is common in HD patients increasing cardiovascular events [188]. Myocardial stunning is common in HD patients, and may contribute to the development of heart failure increasing the mortality in this population. Interestingly, myocardial stunning seems not to be an increased risk on peritoneal dialysis patients despite changes in systemic hemodynamics [189]. Intradialytic recurrent myocardial stunning can cause irreversible fibrotic changes leading to chronic heart failure, arrhythmias and sudden cardiac death [190], that usually has high risk during or after an hemodialysis session. In one study, Jefferies and colleagues found that more frequent hemodialysis associated with decreased incidence of myocardial stunning [191]. In a study performed by Momeni and colleagues (2014) evaluating the relationship between the intradialytic exercise and echocardiographic indices in HD patients found that cardiac systolic and diastolic function in these patients had been improved during HD session [80]. Specifically researchers found an improvement of Left Ventricular Ejection Fraction (LVEF), diastolic function and mitral valve minimum pressure in HD patients after exercise program [80]. Also there are some studies with different results. Previous study of Deligiannis and colleagues (1999) concluded that that supine sub-maximal intradialytic exercise improved the LVEF and maximal oxygen consumption [192] while another study resulted in increasing of cardiac output and decreasing of relative blood volume after intradialytic exercise program [193]. Finally even though the majority of previous studies have shown the beneficial effect of exercise training not only cardiovascular system [183] but also on dialysis efficacy and QOL [194, 195] still·there are many practical burdens to the clinical staff where hesitate to incorporate an intradialytic exercise program into routine clinical practice. Our study is the first to investigate whether exercise training could induce any acute or adverse effect in cardiac functionality and morphology. In the current study no significant changes or adverse effect were found between the two different conditions in Left Ventricular structural data and Ejection Fraction rate implying that the HD-induced myocardial stunning did not change by the implementation of an exercise session. It seems that a single bout of intradialytic exercise is not enough to affect myocardial stunning often seen in hemodialysis patients however, a more intense exercise session could have induce larger changes in the heart.

Conclusions

It seems that our study is the first one to show that a single bout of intradialytic exercise did not affect myocardial stunning often observed in hemodialysis patients. Our data support the notion that aerobic exercise training during hemodialysis is a safe and a well tolerable non-pharmacological approach and does not impose any harmful or adverse effect to patients health or to the hemodialysis therapy per se.

Research Paper 3: The effect of a 9 month intradialytic exercise program on the quality of life, physical performance and fatigue symptoms in hemodialysis patients

Abstract

Introduction: Hemodialysis (HD) patients suffer from generalized weakness, exercise intolerance and muscle atrophy, all leading to a generalized fatigue and a lack of energy. The mechanisms underlying fatigue in these patients are not well understood but from our previous work it has been shown that these should include both intramuscular and central activation failures. Recently it has been shown that the observed impaired daytime functional performance and excessive fatigue do not depend only on muscle atrophy and weakness but are also associated with other factors such as lack of restorative sleep, duration of dialysis sessions, excess weight before dialysis, poor nutritional status, restless legs syndrome and overall mental status of the patients. These factors primarily affect the HD patients' life quality, leading to a vicious circle of fatigue due to inactivity and further inactivity due to fatigue. It is evident that these patients are spending at least 50% of their time, in a functionally "switch off" mode with their fatigue sensations reaching a peak in the immediate hours after the dialysis session.

Aims: The aims of the current study was to assess the effectiveness of a nine month intradialytic exercise program on fatigue symptoms occurring during and after hemodialysis session as well as on functional capacity and quality of life in patients receiving hemodialysis therapy.

Methodology: Twenty stable hemodialysis patients were included in the study (59±13.7 years 16 males). All participants completed a 9-month supervised exercise training program during HD (3 times weekly). Fatigue, sleep quality, depression levels and daily sleepiness status were assessed via validated questionnaires, while functional capacity assessed by a battery of tests, before and after the intervention period.

Results: After the nine month aerobic exercise training intervention, exercise capacity increased by 65% and functional capacity by an average of 40%. Regarding the post dialysis fatigue questions, patients reported feeling better post dialysis after 9 months of exercise training program in the question 1 ($p=0.00$), question 3 ($p=0.009$) and question 4 ($p=0.003$). Nine months of exercise training increased cognitive function ($p=0.037$) and vitality ($p=0.05$) while depressive ($p=0.00$) and fatigue symptoms ($p=0.039$) were found to be significantly improved.

Conclusions: Our study showed that a 9-month aerobic exercise training program improved exercise capacity, depression score and cognitive function followed by a reduction in the severity and the duration

of Post-Dialysis fatigue symptoms while improving the general perception of fatigue. Exercise training is a safe and effective non pharmacological approach to ameliorate fatigue symptoms in HD patients.

Introduction

According to the National Kidney Foundation End Stage Renal Disease (ESRD) is a global health problem [196] and an irreversible progressive condition responsible for high morbidity and mortality [197]. Fatigue is experienced by many patients with a prevalence ranging from 60% to 97% and can be predictor of cardiac events [15]. As in other conditions, in ESRD as well fatigue is often viewed as having a dual nature: central vs. peripheral, brain vs. muscle, physical vs. mental etc. however it has been argued that fatigue in HD patients is more of a 'syndrome' than a single symptom with a complexity and persistence not easily relieved [12]. The hemodialysis (HD) procedure maintains end-stage kidney failure patients alive but as it cannot substitute for a healthy kidney, it heavily taxes the patient's physiology. With regards to skeletal muscle HD patients demonstrate severe atrophy, fat infiltration, and other abnormalities [109]. With regards to cardiovascular health, hemodialysis-induced cardiac injury may trigger intradialytic and post-dialytic arrhythmias [198]. With regards to mental and emotional health, HD patients face an uphill struggle with diminished autonomy and quality of life, often reflected in depression [199] as they enter the vicious cycle of inactivity fed fatigue which leads to diminishing functional capacity.

According to Sakkas and Karatzaferi 2012, fatigue is "*the inability of sustaining an effort either mentally or physically or both while signs and symptoms may be interconnected in a way not always clearly defined* " [12]. The causes of fatigue in HD patients are not well understood but it is been shown that these would include both peripheral (muscular) and central activation failures [200]. HD patients exhibit low levels of physical activity and low functional capacity [201]. Patients report generalized weakness, show exercise intolerance, and muscle atrophy [98], factors that all contribute to an augmented generalized sense of fatigue [13]. Moreover, very often HD patients complain of "brain fogginess" and lethargy [202] especially in the hours post dialysis [203], while ~50% reporting low sleep quality and daily sleepiness [111, 204].

Depending on the assessment tools and the dialysis modality in general undefined fatigue in HD patients has a prevalence from 30 to 80% [132]. Irrespective of instrument used, the average score of fatigue in HD patients is the worst of all chronic disease patients [205] even those with severe depression [206], chemotherapy patients [207], and lupus patients [208].

A factor sometimes overlooked by a patient's environment is that the HD procedure per se [e.g., duration of dialysis sessions [202] etc.,] contributes to fatigue and thus the HD related fatigue adversely affects patients' quality of life [10, 14, 18, 202].

It is noteworthy that one third of HD patients report that they feel worse in the immediate hours after the dialysis session while one out of four reports severe or very severe intensity of fatigue after dialysis [10]. The severity of "Post-dialysis Fatigue" symptoms could range from mild to severe and can last from a few hours after the dialysis procedure up to until the next day [209] or for a "very long time" [10].

When HD patients spent a large proportion of their time in a state of fatigue and since they perceive fatigue (whether in dialysis or in non-dialysis days) as an important barrier in pursuing various life activities [112], the presence of fatigue adversely affects their physical activity levels. Moreover, patients undergoing HD have a high risk for cognitive decline. Conde and her partners found that HD patients presented lower scores at the executive function, attention and memory, with overall cognitive decline being related to the mental aging process [210]. It is not known if cognitive function may contribute to fatigue or if it can be improved by the application of an exercise intervention program.

Moreover, it is not known if emotional intelligence may play a role in fatigue in HD patients. In COPD patients, emotional intelligence was found to be significantly associated to all aspects of quality of life, including fatigue [163].

Delineating fatigue aspects is a difficult task. Many instruments exist, ranging from direct questions to assess the presence of the fatigue sensations [150] to complex questionnaires [211]. Relating fatigue symptoms to physical or mental functional attributes of HD patients hasn't been pursued systematically in the literature. From our group's work and other's [212-214] it is known that depressive symptoms, sleepiness and low quality of sleep may contribute to patient's fatigue. These contributors of fatigue can be greatly improved by improvements in functional capacity, as observed in a study applying a 6 months of aerobic training [215, 216].

Exercise can overall confer many beneficial physiological adaptations that would impact on the patient's quality of life and health [13]. With a view of a holistic approach in reducing fatigue and improving health aspects in HD patients we employed a nine-month moderate intensity exercise intervention in our effort to reduce fatigue in HD patients. To fully address the many aspects of fatigue, and perhaps draw associations to physical attributes, we used instruments designed to assess acute, subacute and chronic

fatigue, with an emphasis on Post Dialysis Fatigue, accompanied by cognitive, emotional and mental health assessments as well as assessments of overall quality of life.

Therefore, the aims of the current study was to assess the effectiveness of a nine month intradialytic exercise program on fatigue symptoms occurring during and after hemodialysis session as well as on functional capacity and quality of life in patients receiving hemodialysis therapy.

Methodology

Study population

Seventy eight patients were assessed for eligibility while only twenty HD patients (16M/4F, 59±13.7 years) (Flow Chart) included in this study. The current project was approved by the Ethics Committee of the University of Thessaly, and by the Bioethics Committee of the local Hospital. All patients gave written informed consent to participate in this study.

Inclusion & Exclusion criteria

Inclusion criteria were: dialysis for at least six months or more with adequate dialysis delivery (Kt/V > 1.1), and with stable clinical condition. Exclusion criteria were: patients unable to give informed consent, opportunistic infection in the last 3 months, malignancy or infection requiring intravenous antibiotics within 2 months prior to enrollment, with HIV, or musculoskeletal contraindication to exercise or requirement for systemic anticoagulation, participating or having participated in an investigational drug or medical device study within 30 days or five half-lives, pregnant, breast feed or female of childbearing potential who did not agree to remain abstinent or to use an acceptable contraceptive regimen. Also, patients who were judged to have clinically significant abnormalities upon clinical examination or laboratory testing, or who were unable to adequately cooperate because of personal or family conditions, or those who suffered from a mental disorder that interferes with the diagnosis and/or with the conduct of the study, e.g. schizophrenia, major depression, dementia were excluded from this study.

HD procedure

The patients underwent the HD therapy (Fresenius 4008B, Oberursel, Germany) 3 times per week with low flux, hollow-fiber dialyzers and bicarbonate buffer. The HD session lasted 4 hours. An enoxaparin dose of 40-60 mg was administered intravenously before the beginning of each HD session. EPO therapy was given after the completion of HD session in order to normalize hemoglobin levels within 11-12 (g/dL).

General Study Design

Patients followed a 9-month aerobic exercise training program implemented during their HD session. The exercise program was supervised by 2 specialized exercise trainers. Cycle exercise was performed 3 times weekly for 60 minutes each time starting between the first 2hr of HD using an adapted cycle

ergometer (Model 881 Monark Rehab Trainer, Varberg, Sweden) at an intensity of 50-60% of the patient's maximal exercise capacity, which was estimated during a previous HD session [145, 146].

During and before release from the HD unit, body mass, systolic and diastolic blood pressures (SBP, DBP) and heart rate (using the RS800CX, Polar Electro Oy, Kempele, Finland) were monitored and recorded. Participants' blood chemistry records were recorded before and at the end of the 9-month study. Participants were assessed in aspects related to exercise capacity, functional ability and strength testing, and were interviewed using standardized questionnaire instruments, designed to assess fatigue aspects (including the sense of chronic or acute fatigue), cognitive function, depressive symptoms, emotional intelligence, pain perception, perceived quality of life, sleep quality and sleepiness, all presented below. The interview approach was employed as to minimize errors due to a possible misunderstanding of a question, to reduce the time needed to collect data as well as to better engage the subjects.

Vital signs measurements

Systolic and Diastolic Blood pressure, Oxygen saturation (SpO_2) and Heart Rate (HR) were measured before, every hour and after the dialysis session. Blood pressure and HR were measured automatic using the HD machines BP system, while SpO_2 was assessed using a fingertip monitor (Onyx II, Nonin Medical, Inc. Plymouth, MN USA).

Anthropometrics and Body composition

The patients' dry weight (ideal weight after removal of excess fluids) was recorded from patients medical record. Together with patients' height it was used to calculate body mass index (BMI).Waist and hip peripheries were measured and the waist to hip ratio (WHR) was calculated. Body composition was assessed using a whole-body multi-frequency bio-impedance spectroscopy system (BCM®, Fresenius Medical Care, Bad Homburg, Germany), to estimate fat mass (FM), lean tissue mass (LTM), total body water (TBW) and body cell mass (BCM) [148]. The body composition measurements were taken immediately before the initiation and after the completion of the HD session and with the participants rested in the supine position. Electrodes were placed on the wrist of the arm without the arterio-venous fistula as well as on the ipsilateral ankle and connected to the BCM device [149].

Blood Chemistry

Routine monthly laboratory results were recorded including C-reactive protein, ferritin, iron, hematocrit, and hemoglobin. The analyses were performed at the clinical biochemistry lab of the University Hospital of Larissa under standard hospital procedures.

Exercise capacity

Using an incremental cycle ergometer test [146] we assessed exercise capacity before, at 3 months, at 6 months and at the end of the 9-month exercise intervention. Values recorded were used to re-adjust the submaximal training intensity of the intradialytic exercise sessions of this program.

Functional Ability

The patient's functional ability levels were assessed via a battery of functional tests: two Sit-to-Stand tests from which three scores were recorded (time taken to complete 5 sit-to-stands STS-5, number of repetitions in 30'' STS-30 and number of repetitions in a whole minute, STS-60).

Handgrip strength

Maximum isometric handgrip strength, (HGS), was measured on the non-fistula (dominant) side [147] before, every hour during a dialysis session and 30 minutes after the end of HD using a handgrip dynamometer (Charder MG4800 Medical Handgrip Dynamometer, Charder Electronic Taiwan). The dynamometer was adjusted so that it fit comfortably to subjects palm size. Before data collection, a warm-up – familiarisation session was performed followed by 2 min rest. Subjects were instructed to grip the dynamometer and apply maximum force in response to a voice command. The subjects stood with both arms extended sideways from the body with the dynamometer facing away from the body. Two trials were performed with a rest period of at least 1 min between trials and the highest HGS value, before and after the HD session, was used in the analyses.

Fatigue

Fatigue was assessed using various questionnaires evaluating chronic, subacute and acute aspects. Acute fatigue was assessed by two questions according to the model proposed by Hardy & Studenski [217]: How tired do you feel right now? What is your energy level right now? The questions asked patients to rate the fatigue and 'energy' on a scale of 0-10 (none to extreme). These questions were asked at before, every hour and after the HD session.

To study the *Quality of General Fatigue* we used the model proposed by Hardy & Studenski [217]. Before the initiation of the HD session, patients answered to six questions about fatigue quality (Q1-

Tiredness: Do you feel tired much of the time? Q2-Emotional: Do you feel that life is empty? Q3-Cognitive: Do you have trouble concentrating? Q4-Sleepiness: Have you had difficulty sleeping in the past month? Q5-Weakness: Have you had muscle weakness in the past month? Q6- Lack of energy: Do you feel full of energy?). Each patient was invited to answer "yes" or "no" to these questions (for the subsequent analysis a yes = 1, and a no=0).

Post dialysis fatigue was assessed by a questionnaire by Sklar et al. [9]. The questionnaire asks patients to rate the frequency of postdialysis fatigue on a scale of 0-5 (never to very often); the severity, on a scale of 1-5 (very mild to very severe); and the duration on a scale of 1-5 (a very short time to a very long time).

Moreover, chronic general fatigue was assessed by Fatigue Severity Scale (FSS) [218]. This questionnaire contains nine statements concerning respondent's fatigue to measure fatigue severity. Additionally, we used the Multidimensional Fatigue Inventory (MFI) [219] which is a 20-item scale designed to evaluate in general the dimensions of general fatigue, physical fatigue, reduced motivation, reduced activity, and mental fatigue. For subacute fatigue, we used the Brief Fatigue Inventory (BFI) [151] which is an instrument that can be administered in a clinical setting to assess the severity of fatigue experienced by patients, as well as its impact on their ability to function over the previous 24h.

Cognitive Function

Cognitive Function was assessed by the Mini Mental State Exam (MMSE) [220] which is a brief 30-point questionnaire test that is used to screen for cognitive impairment. This test consists of simple questions and problems in a number of areas: the time and place of the test, repeating lists of words, arithmetic such as the serial sevens, language use and comprehension, and basic motor skills. For example, one question, derived from the older Bender-Gestalt Test, asks to copy a drawing of two pentagons.

Symptoms of Depression

Depressive symptoms were measured using the Zung Self Rating Depression Scale (with a score > 44 being considered the cut-off for diagnosis of depression). Moreover, we used the Beck Depression Inventory II (Beck Depression Test, BDT) [154] to assess the intensity of depression.

Emotional Intelligence

Emotional intelligence was assessed by using the Schutte Self Report Emotional Intelligence Test (SSEIT) [155]. This instrument is a 33 item self-report and patients are asked to indicate their responses

to items reflecting adaptive tendencies toward emotional intelligence according to a 5-point scale, with "1" representing strong agreement and "5" representing strong disagreement.

Wong and Law Emotional Intelligence Scale (WLEIS) [156] is a shorter instrument, which contains 16 items grouped in four subscales as follows: (a) self-emotion appraisal (SEA), (b) emotion appraisal of others (OEA), (c) use of emotion (UOE), and (d) regulation of emotion (ROE).

Pain perception

In addition each subject also completed the Fibromyalgia Impact Questionnaire (FIQ) [157]. This self-administered questionnaire developed to measure fibromyalgia (FM) patient status, progress and outcomes. The instrument contains 11 questions measuring physical functioning, work status (missed days of work and job difficulty), depression, anxiety, morning tiredness, pain, stiffness, fatigue, and well-being over the past week.

Perceived Quality of Life

Quality of life was assessed by the Generic Medical Outcomes Survey 36 Item–Short Form (SF-36) [158] that contains eight dimensions, generating a profile of health-related quality of life. These dimensions are: 1) Physical Functioning; 2) Role Limitations due to Physical Functioning; 3) Bodily Pain; 4) General Health Perceptions; 5) Vitality; 6) Social Functioning; 7) Role Limitations due to Emotional Functioning; and 8) Mental Health. Total SF36 QoL score ranges from 0 (extremely poor) to 100 (very good). Moreover, the quality of life in the clinical setting was evaluated by the Missoula-Vitas Quality of Life Index Version-15R. The MVQOLI is an assessment instrument that gathers patient - reported information about quality of life during advanced illness. We used the short version of 15-items questionnaire for dialysis patients [159].

Sleep and sleepiness

We evaluated possible sleep disturbances and usual sleep habits during the preceding month by the Pittsburgh Sleep Quality Index (PSQI) which contains 19 questions [160].

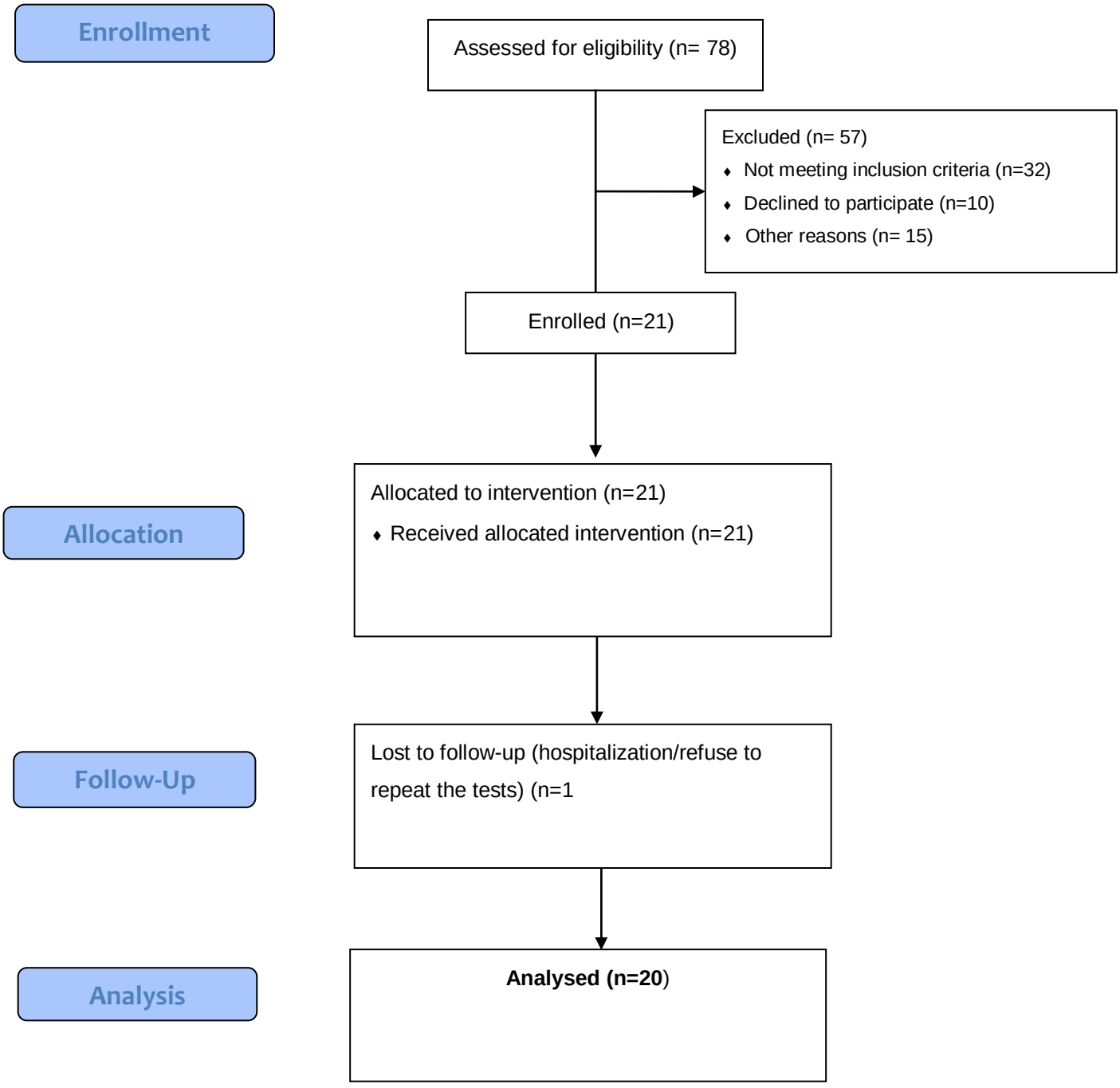
Furthermore, the HD patient's daily sleepiness status was assessed by using the Epworth sleepiness scale (ESS) [161]. This scale differentiates between average sleepiness and excessive daytime sleepiness that requires intervention.

Statistical analysis

The results are expressed as mean ± SD. In some instances delta values of the differences between pre- and post-dialysis values are presented. Statistical analysis was performed using two-way repeated measures analysis of variance (ANOVA). For comparing initial and final values (pre and post exercise training) paired t tests were used. All the statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS for Windows, version 18.0, Chicago III). Differences were considered significant when $P \leq 0.05$.

Results

Flow Chart



All twenty HD patients who participated in the study completed the 9-month intervention without any adverse effects. Patient anthropometric characteristics, as well as routine blood biochemistry and body composition values are presented in Table 1. There were no statistically significant differences between pre and post exercise training program values in these patient characteristics.

Table 1. Hemodialysis patient anthropometric characteristics, routine blood biochemistry indices and body composition values. All data are mean ± SD. No significant differences

Variables	**Pre**	**9 months later**
N	20	20
Female/Male	4/16	4/16
Dry Weight (kg)	72.7±13.5	73.9±13.9
Height (m)	1.7±0.1	1.7±0.1
BMI (kg/m^2)	25.6±4.3	26.0±4.6
Steps per week	49158.6±26770.6	44585.9±31925.6
Months in dialysis	52.8±47.1	61.8±47.1
Kt/V	1.60±0.50	1.48±0.31
CRP(mg/dL)	1.9±3.8	1.2±3.0
HCT	34.1±3.6	33.5±2.7
Hb(g/dL)	11.0±1.2	10.7±0.8
Iron(μg/dL)	53.8±25.3	59.6±32.9
Ferritin (ng/mL).	502.6±822.5	467.9±491.1
WHR	1.0±0.1	1.0±0.1
Total Fat (kg)	23.4±10.4	21.2±9.7
TBW (L)	35.1±6.0	36.0±6.8
LTM (kg)	42.3±10.0	43.5±9.4
BCM (kg)	24.1±24.3	25.0±6.5

BMI, Body mass index; CRP, C Reactive Protein; HCT, hematocrit; Hb, hemoglobin; WHR, waist to hip ratio; Kt/V, dialysis efficiency;TBW, total body water; LTM; lean tissue mass; BCM, body cell mass.

Exercise capacity was assessed using a cycle ergometer test at 4 time points during the study, i.e. before, at 3 months, 6 months and at the conclusion of the 9-month training program. It increased throughout the study, reaching a 1.6 fold increase by the end of the study (Fig 1).

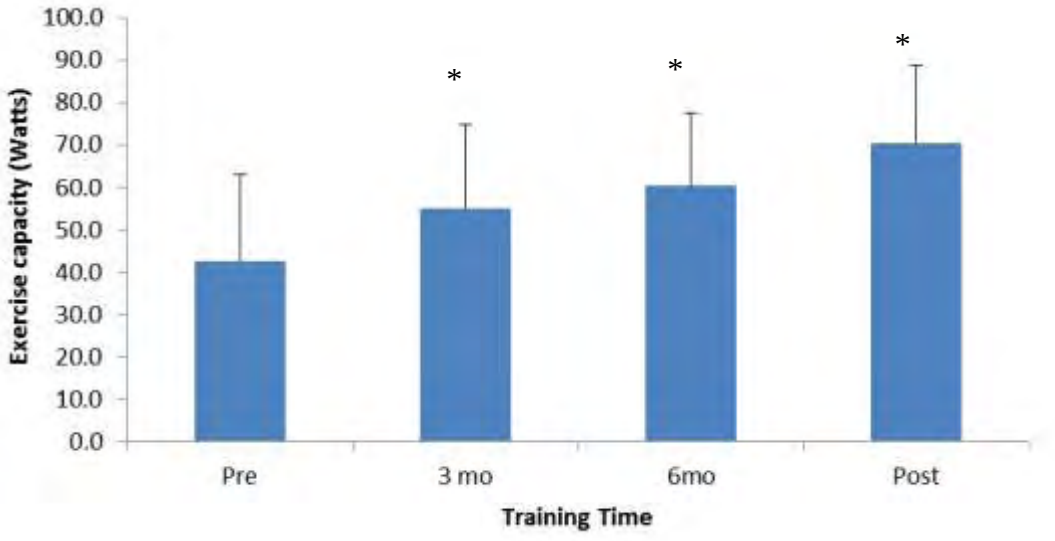


Figure 1. Changes in exercise capacity during the 9-month aerobic exercise training period.* $p<0.01$ from pre-training values.

During an HD session the change in hemodynamics was reflected by the fluctuation in blood pressure. While no statistically significant differences were observed in SBP between pre and post 9-month training values (Fig.2), we observed a tendency for improvement in maintaining DBP which reached statistical significance at 30min post-dialysis (Fig.3).

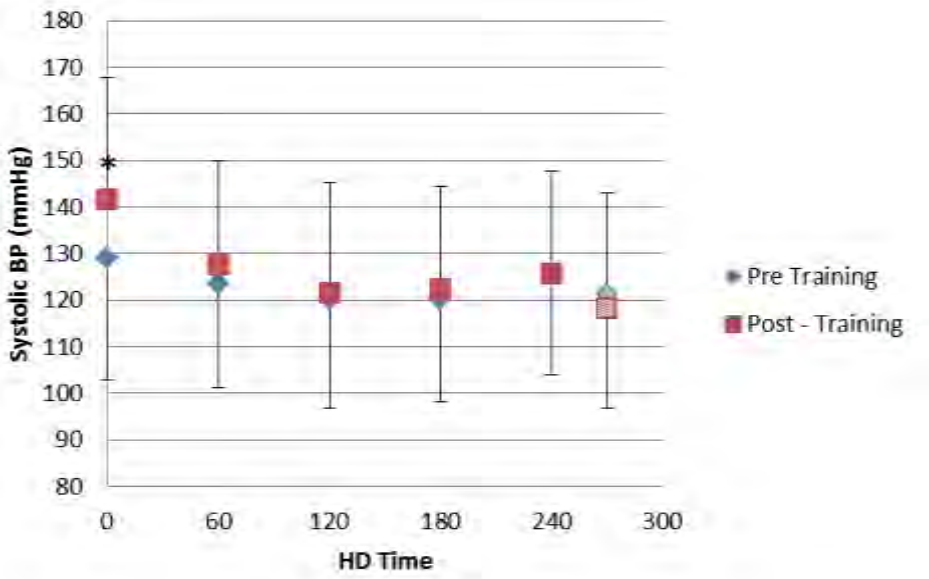


Figure 2. Systolic blood pressure pre (in blue) and post (in red) 9 months training at different time points during 4 hrs of HD and at 30 min post dialysis (lighter symbols). Note that the value at 120 min was influenced by the preceding 60 min of exercise training. Values are presented as Mean ± S.D. * $p<0.05$ from corresponding value before the training program.

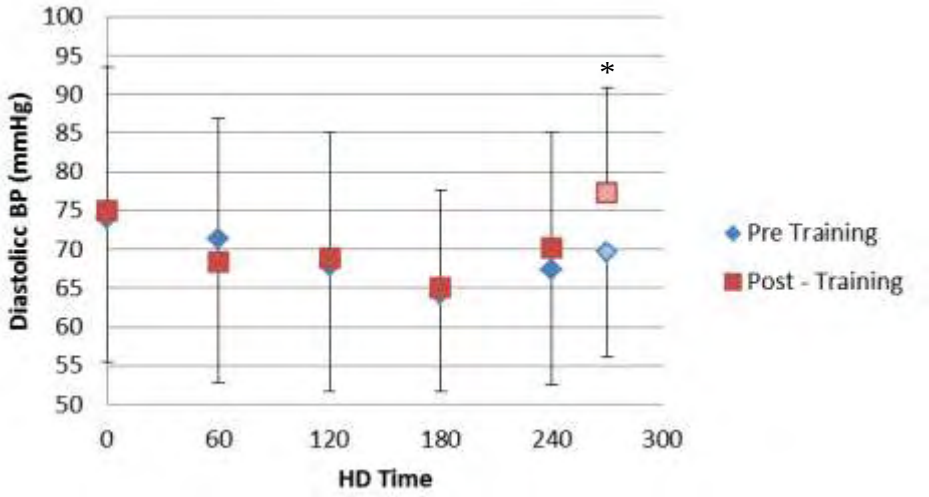


Figure 3. Diastolic blood pressure pre (in blue) and post (in red) 9 months training at different time points during 4 hrs of HD and at 30 min post dialysis (lighter symbols). Note that the value at 120 min

was influenced by the preceding 60 min of exercise training. Values are presented as Mean ± S.D. * $p<0.05$ from corresponding value before the training program.

Averaged Heart rate values at different time points of the HD session were influenced by the 9-month training program at at 2nd and 3rd hours of HD (Fig 4). Oxygen saturation tended to be overall better maintained with values differing statistically significantly at the conclusion of the 4th hour of HD (Fig 5).

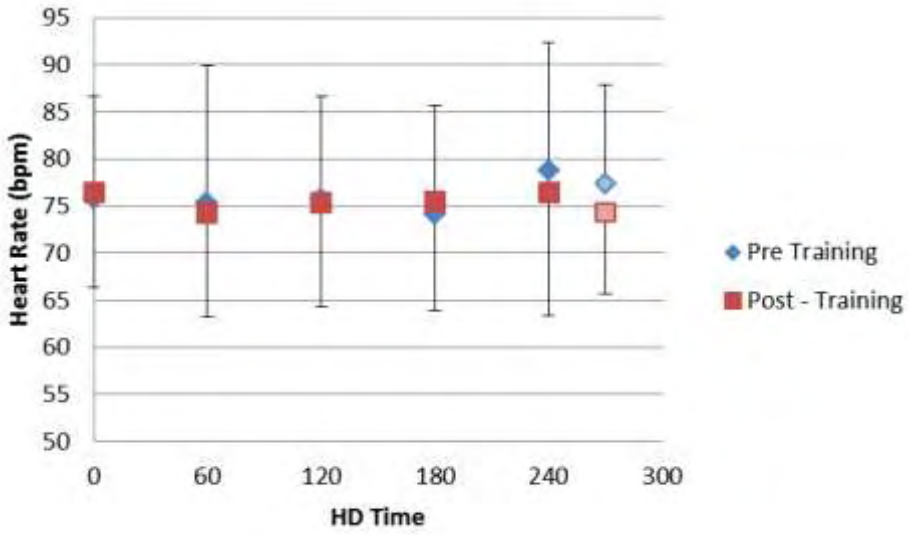


Figure 4. Heart rate recorded pre (in blue) and post (in red) 9 months training at different time points during 4 hrs of HD and at 30 min post dialysis (lighter symbols). Note that the value at 120 min was influenced by the preceding 60 min of exercise training. Values are presented as Mean ± S.D.

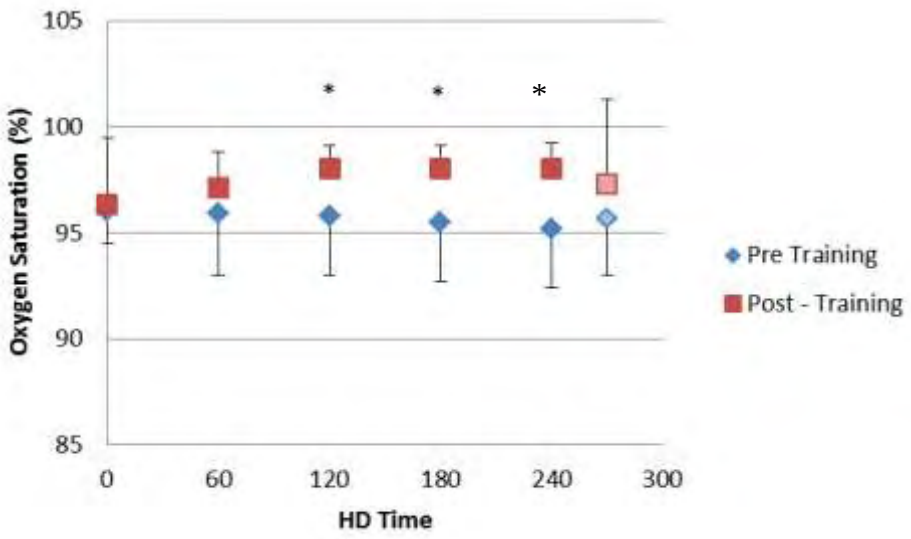


Figure 5. Oxygen saturation (SpO_2%) recorded pre (in blue) and post (in red) 9 months training at different time points during 4 hrs of HD and at 30 min post dialysis (lighter symbols). Note that the value at 120 min was influenced by the preceding 60 min of exercise training. Values are presented as Mean ± S.D. * $p<0.05$ from corresponding value before the training program.

Handgrip muscle strength didn't fluctuate a lot during the HD session. However, while the exercise program stressed the lower body, baseline handgrip strength was significantly higher after the 9 months of training (Fig 6).

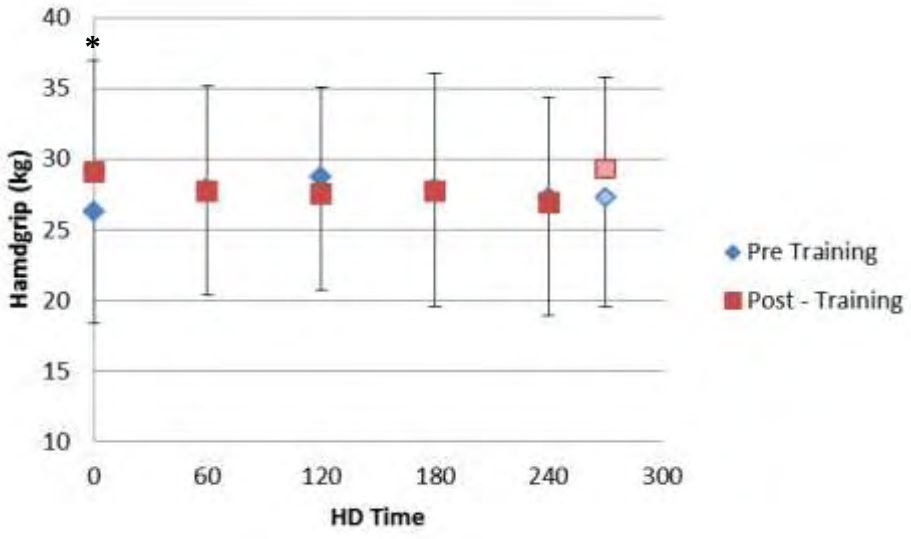


Figure 6. Handgrip muscle strength recorded pre (in blue) and post (in red) 9 months training at different time points during 4 hrs of HD and at 30 min post dialysis (lighter symbols). Note that the value at 120 min was influenced by the preceding 60 min of exercise training. Values are presented as Mean ± S.D. * $p<0.05$ from corresponding value before the training program.

As expected HD resulted in an overall acute improvement in functional ability of the subjects as reflected by the performances in the STS tests. Following the 9 months training intervention, functional ability was overall improved in agreement to the already reported increase in exercise capacity.

The time needed to complete 5 sit-to stand repetitions (STS5), an estimate of muscle power, was significantly improved by the training intervention whether at the pre-HD state (12.9±4.9 *vs* 9.4±3.2 reps, $p<0.05$) or at the post-HD state (13.0±5.4 *vs* 9.9±3.2 reps, $p<0.01$).

In terms of muscular endurance, STS30 and STS60 scores significantly improved after 9 months of aerobic exercise training (Figs 7 and 8).

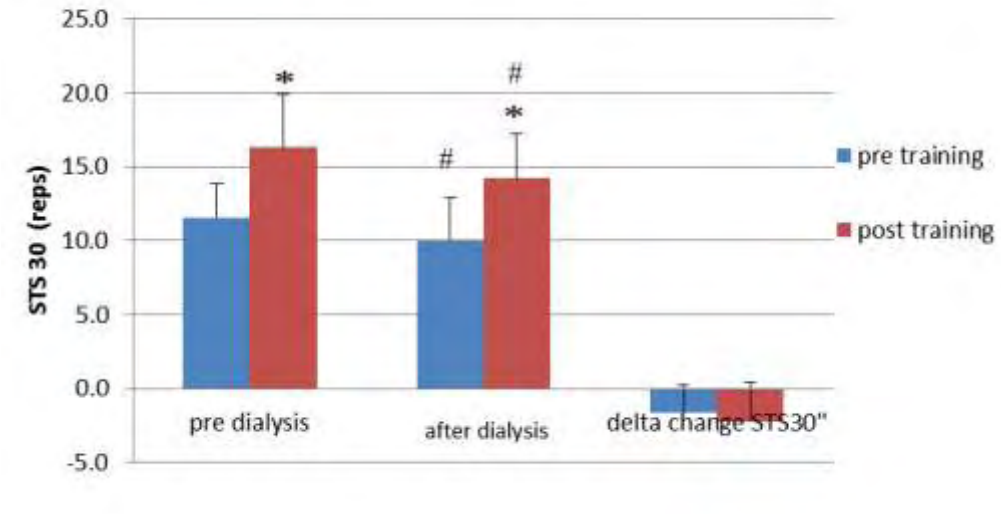


Figure 7. Performance (repetitions) in the sit-to-stand for 30 sec (STS30) test before (in blue) and after (red) the 9 months training, before and after a dialysis session. The calculated delta difference between

pre and post dialysis scores are also presented. Data are presented Mean ± SD. * p<0.05 from pre-training value, # p<0.05 from corresponding pre-dialysis value.

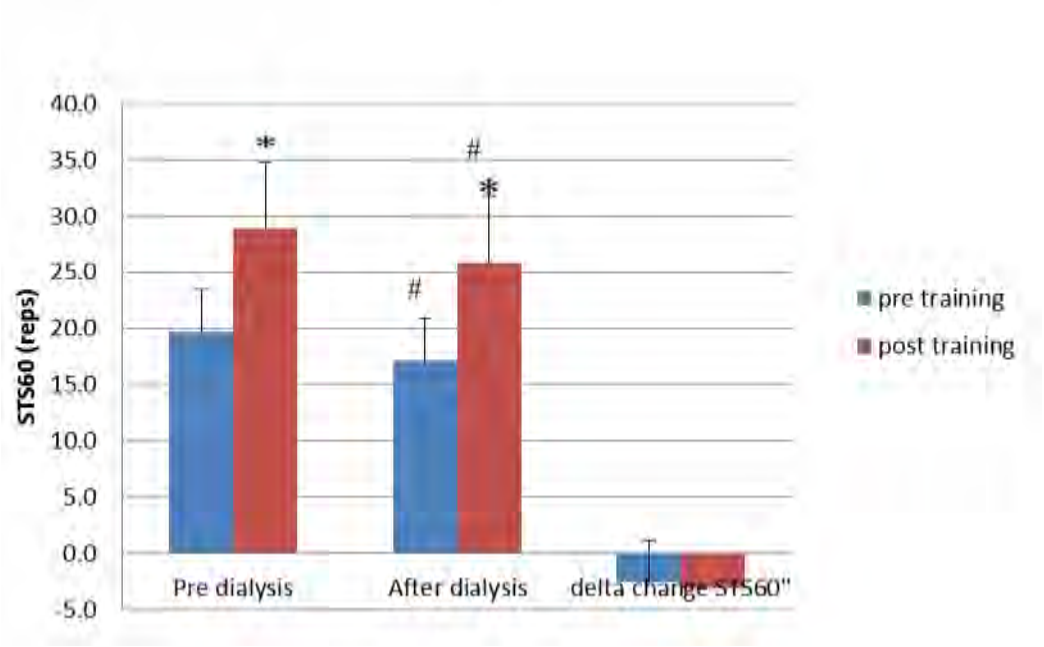


Figure 8. Performance (repetitions) in the sit-to-stand for 60 sec (STS60) test before (in blue) and after (red) the 9 months training, before and after a dialysis session. The calculated delta difference between pre and post dialysis scores are also presented. Data are presented Mean ± SD. * p<0.05 from pre-training value, # p<0.05 from corresponding pre-dialysis value.

With regards to an acute sense of fatigue there were no statistically significant differences between values reported before and after the 9 month exercise intervention, despite a tendency for overall lower scores in rating the question "How tired do you feel right now?". Additionally no differences were found in the responses to the question "What is your energy level right now?" (refer to Table 2, top two rows of data).

Regarding the Quality of general fatigue, "Tiredness" remained the highly scored quality, but no differences were observed after training (refer to Table 2, top rows of data 3 to 8). With regards to Post Dialysis Fatigue, the training programme significantly affected some aspects, notably severity and duration (refer to Table 2, bottom 4 rows of data).

Table 2. Effects of 9 months exercise training on acute and subacute sense of fatigue and post-dialysis fatigue (PDF). All data are Mean ± SD.

Assessment	Training	Pre HD	1st HD hr	2nd HD hr	3rd HD hr	4th HD hr	30 min after HD
Fatigue Now	Pre	2.6±2.1	2.6±2.1	3.1±2.4	3.6±2.4	3.9±2.3	
	Post	1.5±1.9	1.7±2.6	1.5±2.2	2.5±2.8	3.4±2.6	
Energy Now	Pre	6.3±1.5	6.4±1.6	6.3±1.8	5.7±1.7	5.2±1.6	
	Post	7.1±2.2	6.1±3.3	6.1±3.1	6.1±2.9	5.9±2.6	
GF-1-Tiredness	Pre	2.0±0.2					
	Post	2.0±0.2					
GF-2-Emotional	Pre	1.9±0.3					
	Post	1.9±0.4					
GF-3-Cognitive	Pre	1.8±0.4					
	Post	1.8±0.4					
G5-4-Sleepiness	Pre	1.9±0.4					
	Post	1.6±0.5					
GF-5-Weakness	Pre	1.7±0.5					
	Post	1.6±0.5					
GF-6-Lack of energy	Pre	1.3±0.5					
	Post	1.6±0.5					
Q 1-PD status	Pre						2.7±0.5
	Post						**2.0±0.5
Q 2 –PDF frequency	Pre						1.7±0.6
	Post						1.4±1.0
Q 3 –PDF severity	Pre						1.7±0.6
	Post						*1.3±0.6
Q 4 –PDF duration	Pre						1.8±0.7
	Post						*1.1±0.8

Questions on acute fatigue, Fatigue now: How tired do you feel right now? Energy now: What is your energy level right now? Questions on Quality of General Fatigue (GF) according to [217]. GF- 1: Do you feel tired much of the time? GF- 2: Do you feel life is empty? GF- 3: Do you have trouble

concentrating? GF- 4: Have you had difficulty sleeping I the past month? GF- 5: Have you had muscle weakness in the past month? GF- 6: Do you feel full of energy?
PD fatigue was assessed according to (Sklar, Riesenberg, Silber, Ahmed, & Ali, 1996)
PD-Q 1: How do you feel after dialysis? PD-Q 2: How often do you experience postdialysis fatigue? PD-Q 3: How severe is your postdialysis fatigue? PD-Q 4: How long does your fatigue last for?
** p<0.05 from corresponding value before the 9 months training; **p<0.01 from corresponding value before the 9 months training*

With regards to cognitive function a small in magnitude but statistically significant improvement was observed, accompanied by a significant reduction in the depressive symptoms according to the Zung Self Rating Depression Scale, ZSDS (see Table 3).

Notably, regarding chronic fatigue, the score in the Multi-Dimensional Fatigue Inventory (MFI) was significantly reduced after 9 months of aerobic training, accompanied by a significant reduction in the Fibromyalgia Impact Questionnaire (FIQ) scores (see Table 3).

Regarding the patients' quality of life, the Missoula-VITAS Quality of Life Index assessment did not significantly change, nor the scores in sleep quality and sleepiness by the 9 months of training (see Table 3)

Table 3. Effects of 9 months of aerobic exercise on cognitive function (MMSE), depressive symptoms (ZSD, BDI), chronic fatigue (FSS, MFI, BFI), emotional intelligence (WLEIS, SSEIT), pain perception (PAIN, FIQ) and quality of life indices (Vitality, Physical and Mental Health from SF-36, and MVQOLI), sleepiness (ESS) and sleep (PSQI). All data are mean ± SD.

	Pre-training	Post-training	p values
MMSE	26.2±1.9	26.7±2.1	***0.037**
ZSDS	41.3±6.0	23.7±7.5	****0.000**
BDI	5.00±4.8	7.7±7.2	0.077
FSS	3.6±1.2	3.5±1.5	0.841
MFI	47.7±10.5	38.6±17.9	***0.039**
BFI	1.4±1.2	1.8±1.7	0.203
WLEIS	89.2±9.1	87.9±12.8	0.749
SSEIT	128.6±12.0	133.0±15.4	0.402
FIQ	15.2±4.8	8.1±5.8	****0.000**
SF36 QoL Vitality	57.1±12.4	65.3±14.1	***0.050**
SF36 QoL PCS	65.3±17.5	67.0±17.6	0.596
SF36 QoL MCS	64.7±10.9	64.1±12.3	0.872
SF36 QoL Total	69.3±13.1	66.8±15.4	0.462
MVQOLI	18.3±3.4	18.8±3.0	0.555
ESS	4.3±2.5	6.0±3.0	0.137
PSQI	5.5±3.0	6.1±5.0	0.610

MMSE, Mini Mental State Exam; FSS, Fatigue Severity Scale; WLEIS, Wong and Law Emotional Intelligence Scale; SSEIT, Schutte Self-Report Emotional Intelligence Test; FIQ; Fibromyalgia Impact Questionnaire, ZSDS, Zung Self Rating Depression Scale; BDI; Beck Depression Inventory; MFI, Multi-Dimensional Fatigue Inventory; BFI, Brief Fatigue Inventory; MVQOLI, Missoula-VITAS Quality of Life Index; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; QoL; quality of life

** p<0.05 from corresponding value before the 9 months training; **p<0.01 from corresponding value before the 9 months training*

Discussion

Our study showed that a 9-month aerobic exercise training program ameliorates the severity and the duration of Post-Dialysis fatigue symptoms. It also showed that it improved the general perception of fatigue.

This was the first study in hemodialysis patients, to our knowledge, designed to assess both acute and chronic aspects of general fatigue as well as the presence and severity of post-dialysis fatigue in combination with physical, mental and QoL assessments in an attempt to better explain fatigue and investigate the benefits of an exercise program in ameliorating fatigue, and preventing mental or other deficits.

Hemodialysis related fatigue significantly affects patients' quality of life as suggested by many authors [10, 14, 18, 202]. The improvement in Post Dialysis Fatigue, presence, severity and duration, that we observed in this study is perhaps mediated by the recorded improvements in exercise capacity, muscle strength and functional ability which in turn reflect an improved physical status of the patients and perhaps a better stamina towards the fatiguing effects of dialysis per se. Previous studies from our group and others [221] have indicated the beneficial effects of this type of exercise on cardiovascular, cardiorespiratory and neuromuscular function of the patients. Moreover, in another study (*to be published/ see Chapter 4*), we reported that 9 months of exercise improve hemodynamic responses and confer favorable adaptations to the heart structure, leading to better ejection fraction and overall improved cardiac function. All these adaptations can help a patient tolerate the dialysis session better and maintain a better post-dialysis physical and mental functional status.

Given the importance of preventing cognitive impairment with ageing in order to avoid a loss of independence and premature death, it is notable that in our study, 9 months of moderate intensity aerobic training statistically improved cognitive function in HD patients. This is of crucial importance for HD patients as they have been reported to perform poorly in cognitive assessment in comparison to other patient groups [210]. Physical activity is beneficial for cognitive function especially in elderly humans and it has been shown to prevent brain atrophy in many conditions [222-224]. Many physiological mechanisms have been proposed to explain the influence of physical activity on cognition, focusing mostly on changes in neurotransmitters, neurotrophins and vasculature [225] Chronic renal failure patients present with depressive symptoms while previous studies have indicated that cognitive

impairment is highly correlated with depression [226]. In our study a 9-month exercise program, significantly reduced the depressive symptoms according to the Zung Self Rating Depression Scale. This finding is in agreement to previous findings [199, 215] and further underlies the important role that exercise can play in improving mental health in chronic patients.

Notably, regarding chronic fatigue, the score in the Multi-Dimensional Fatigue Inventory (MFI) was significantly reduced after 9 months of aerobic training.

Regarding the patients' quality of life, from the SF36-QoL assessment only the aspect of Vitality were influenced by the 9 months of training, while the score in Missoula-VITAS Quality of Life Index did not significantly change. The observed significant increase in the vitality of the SF36, has been also found in previous studies [146]. Exercise training in our study did not improve daily sleepiness levels, confirming previous data [146, 227].

However, and notably, the scores in the Fibromyalgia Impact Questionnaire were improved, meaning that patients enjoyed more pain free time during everyday activities.

Conclusions

In conclusion our study showed that a 9-month aerobic exercise training program improved exercise capacity, depression score and cognitive function followed by a reduction in the severity and the duration of Post-Dialysis fatigue symptoms while improving the general perception of fatigue. Exercise training is a safe and effective non pharmacological approach to ameliorate fatigue symptoms in HD patients by improving all aspects of health related quality of life.

Research Paper 4: The effect of a nine month intradialytic exercise training program on myocardial stunning in hemodialysis patients

Abstract

Introduction: Cardiovascular disease is the most common cause of death in HD patients. Sudden cardiac death also occurs in this population due to decreased heart rate variability. Exercise training has beneficial effect for cardiovascular fitness and reducing mortality in ESRD. Whether there is a long term benefit of exercise during HD on a reduction in myocardial stunning is not known.

Aims: The aim of the study was to investigate the effect of a nine month intradialytic exercise training programme on myocardial stunning in patients on hemodialysis.

Methodology: Twelve stable HD patients (10M/2F, 58±16yrs) participated in the study. At baseline and after 9 months in the study, all patients underwent echocardiography, conducted by examiners. Echocardiographic scans were performed using an iE33 echocardiographic system. All images were acquired with the subject lying in the left lateral decubitus position with a 2.5 MHz transducer. Myocardial stunning was assumed when a >20% reduction in ejection fraction was observed. Generalized linear model (GLM) repeated measures were used to compare the difference in echocardiographic indices after 9 months of exercise intervention.

Results: Ejection Fraction (EF) improved significantly after 9 months of exercise training compared to the baseline value (48.7±11.1 vs 58.8±6.5, p=0.046). Additionally, at the end of hemodialysis session were observed differences in EF% (50.0±13.4 vs 56.1±3.4, p= 0.054) and deceleration time (261.1±61.9 vs 215.0±50.5, p=0.014).

Conclusions: Our results showed that after the 9 month exercise intervention program, a significant improvement in ejection fraction by 21% was observed. Intradialytic exercise training can become a non-pharmacological approach to reduce myocardial stunning induced by the hemodialysis therapy. New protocols with longer training periods are required to assess the effect of exercise on clinical outcomes.

Introduction

Conventional hemodialysis (HD) therapy itself has been associated with various cardiovascular abnormalities and cardiovascular stress [228]. Hemodialysis-induced myocardial stunning (cardiac injury) is a common phenomenon in the HD patients and is associated, inter alia, with cardiac dysfunction, increased risk for developing cardiovascular disease or even with increased mortality and morbidity [229]. It is reported that approximately two thirds of the HD population experience recurrent hemodialysis-induced cardiac injury [228]. On the other hand, it is known that the hemodialysis patients are exposed to increased risk for cardiac arrhythmias leading to sudden cardiac death [230], whilst hemodialysis-induced cardiac injury may trigger intradialytic and post-dialytic arrhythmias [198]. Previous research has suggested that the reduced heart rate variability (HRV) which characterize the majority of the HD population may play an important role in the higher risk of sudden cardiac death [231]. Interestingly, exercise training has been proven to induce beneficial effect on the cardiovascular system of the HD patients, reducing among others, cardiovascular events and improving autonomic function by increasing HRV [232], whilst increases in parallel left ventricular ejection fraction [80, 192], stroke volume and cardiac output [192].

The primary aim of this study was to investigate the effect of a nine month intradialytic exercise training programme on myocardial stunning in patients on hemodialysis. Secondary aims were to examine potential associations between myocardial stunning indices, heart rate variability and body composition in the same group of patients during the intervention period.

Methodology

Ethics Statement

The study was approved by the Human Research and Ethics Committee of the University of Thessaly, and by the bioethics committee of the University General Hospital of Larissa, and the General Hospital of Trikala, Greece. All patients gave their written informed consent prior to study participation.

Study population

Seventy eight patients were assessed for eligibility while only twelve HD patients (10M/2F, 56±19yrs) participated in the study (Flow Chart). Patients were recruited from the HD unit of the local hospital and all testing was performed on site in the hospital between April 2014 and May 2015. The inclusion criteria for the study were: being on HD for at least three months or more with adequate dialysis delivery and with stable clinical condition. Exclusion criteria included: (1) absence of diagnosed neuropathies (2) presence of a catabolic state within 3 months prior to the start of the study, (3) or unable or refusal to participate in an exercise training programme. None of the recruited patients were engaged in any systematic exercise training programme, 3 months prior the initialization of the study. After the initial screening, twelve patients fulfilled the criteria and enrolled to the study (see Table 1). The study was approved by the Human Research and Ethics Committee of the University of Thessaly, and by the bioethics committee of the University General Hospital of Larissa, Greece (UHL). All patients gave their written informed consent prior to study participation.

Study Design

Patients followed a 9-month intradialytic exercise training program (exercise took place during the HD session). The exercise program was supervised by 2 specialized exercise physiologists. Supine cycle exercise was performed 3 times weekly for 60 minutes each time during the first 2 hours of HD session using an adapted bicycle ergometer (Model 881 Monark Rehab Trainer, Varberg, Sweden) at an intensity of 50-60% of the patient's maximal exercise capacity (W), which was estimated during a previous HD session [233]. All examined parameters were assessed pre and post the 9 month intervention period.

During both examinations, the Echocardiographic and HRV indices were collected before the initialization of the HD session, during the last hour of the HD session and after the end of the HD session while patients were rested on the bed.

HD procedure

The patients underwent the HD therapy (Fresenius 4008B, Oberursel, Germany) 3 times/week with low flux, hollow-fiber dialysers and bicarbonate buffer. Each HD session lasting approximately 4 hours. An enoxaparin dose of 40-60 mg was administered intravenously before the beginning of each HD session. EPO therapy was given after the completion of HD session in order to normalize hemoglobin levels within 11-12 (g/dL).

Body composition assessment

Body composition was measured by a whole-body multi-frequency bio-impedance spectroscopy system (BCM®, Fresenius Medical Care, Bad Homburg, Germany). This system estimates fat mass (FM), lean tissue mass (LTM), total body water (TBW) and body cell mass (BCM) [148]. The body composition measurement were taken immediately before and with the participants rested in the supine position (Table 1). Electrodes were placed on the wrist of the arm without the arterio-venous fistula as well as on the ipsilateral ankle and connected to the BCM device [149].

Echocardiography

Echocardiographic scans were performed using an iE33 echocardiographic system (Philips Medical Systems, Andover, MA, USA). All image acquisitions were made with the subject lying in the left lateral decubitus position using a 2.5 MHz transducer. For each patient, ≥ 3 consecutive beats were analyzed in each scan, and the mean value was used in the subsequent statistical analysis. All echocardiograms were performed by the same experienced echocardiographer. For the recording of HR, a single lead ECG inherent to the echocardiographic system was used. Left ventricular dimensions were determined from 2-dimensional guided M-Mode images according to the recommendations of the American Society of Echocardiography (ASE) for chamber quantification, [186] using the parasternal long-axis acoustic window. LV mass was calculated from M-Mode traces at the level of mitral valve and determined in g by

using the recommended ASE formula. LV mass index was calculated by dividing LV mass by body surface area (using the DuBois and DuBois formula) and height [187] to minimize effects of age, gender, and overweight status [186]. For the assessment of LV diastolic function, the transducer was applied apically (4-chamber view) whilst a pulsed wave Doppler sample volume (4 mm) was located at the tips of the mitral valve leaflets. Doppler gain, pulse repetition frequency, and high-pass filter were all adjusted in order to maximize the signal to noise ratio. The following parameters were evaluated: early peak flow velocity (E), late peak flow velocity (A); thus the ratio of E to A was calculated. The primary outcome variable was ejection fraction (EF) (index used to assess myocardial stunning) and change in ejection fraction (ΔEF) from baseline to intervention. Ejection fraction was calculated using the biplane Simpson's method from 2-dimensional apical 2- and 4- chamber orientation to evaluate the patient's systolic function.

HRV Assessment

Heart rate variability was measured using heart rate monitors (RS800CX, Polar Electro Oy, Kempele, Finland) validated for heart rate variability assessment [234]. For the heart rate variability time domain, the square root of the mean of squared differences between successive RR intervals and the percentage of successive normal-to-normal intervals greater than 50 milliseconds were computed [235]. For the heart rate variability frequency domain, the low and high frequency bands, expressed in normalised units (nu), and their ratio (low frequency/high frequency) were reported [235]. Heart rate variability indices (low frequency activity, high frequency activity, low frequency/high frequency activity, the square root of the mean of squared differences between successive RR intervals, and the percentage of successive normal-to-normal intervals greater than 50 milliseconds) were analyzed using heart rate variability Analysis Software V1.1 (Finland; Biomedical Signal Analysis Group, University of Kuopio, Finland 2002).

Blood Chemistry

Routine monthly laboratory results were recorded including c reactive protein, ferritin, iron, hematocrit, and hemoglobin. The analyses were performed at the clinical biochemistry lab of the University Hospital of Larissa under standard hospital procedures.

Exercise capacity

Using an incremental cycle ergometer test [146] we assessed exercise capacity before, at 3 months, at 6 months and at the end of the 9-month exercise intervention. Values recorded were used to re-adjust the submaximal training intensity of the intradialytic exercise sessions of this program.

Functional Capacity

The patient's functional ability levels were assessed via two Sit-to-Stand tests from which three scores were recorded (time taken to complete 5 sit-to-stands STS-5, number of repetitions in 30'' STS-30 and number of repetitions in a whole minute, STS-60).

Handgrip strength

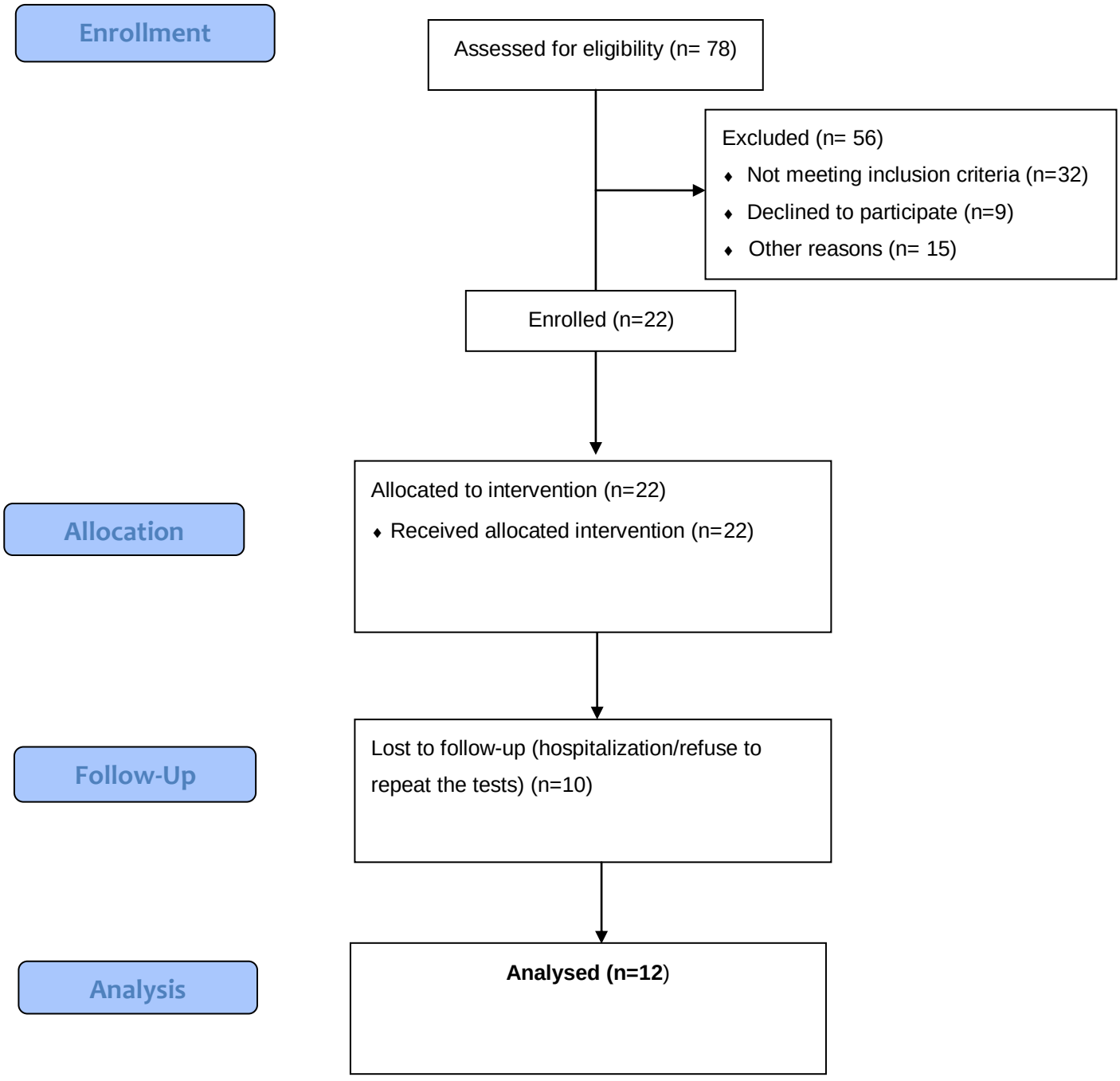
Maximum isometric handgrip strength, (HGS), was measured on the non-fistula (dominant) side [147] before, every hour during a dialysis session and 30 minutes after the end of HD using a handgrip dynamometer (Charder MG4800 Medical Handgrip Dynamometer, Charder Electronic Taiwan). The dynamometer was adjusted so that it fit comfortably to subjects palm size. Before data collection, a warm-up – familiarisation session was performed followed by 2 min rest. Subjects were instructed to grip the dynamometer and apply maximum force in response to a voice command. The subjects stood with both arms extended sideways from the body with the dynamometer facing away from the body. Two trials were performed with a rest period of at least 1 min between trials and the highest HGS value, before and after the HD session, was used in the analyses.

Statistical analysis

Statistical analysis was performed using two-way repeated measures analysis of variance (ANOVA). For comparing initial and final values (pre and post exercise training) paired t test were used for parametric and non-parametric data. The Kendall's product-moment correlation was used to assess the relationship between the body composition and echocardiographic indices. The results are expressed as mean ± SD. All the statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS for Windows, version 18.0, Chicago III). The level for statistical significance was set at $P \leq 0.05$.

Results

Flow Chart



Patient basic characteristics are presented in Table 1. All twelve hemodialysis patients who participated in the study completed the f 9-months intervention program without any adverse effects.

Table 1. Hemodialysis patient basic characteristics before and after nine months of intradialytic exercise training

Variables	**Pre**	**Post**
N	12	12
Female/Male	2/10	
Age (yr)	58±16	
Dry Weight (kg)	73.2±16.4	75.4±16.9
Height (m)	1.69±0.10	1.69±0.10
BMI (kg/m^2)	26.1±5.2	26.9±5.5
Steps per week	52082.3±27749..4	43091.1±31076.1
Months in dialysis	40±44	
WHR	10.2±0.12	1.00±0.1
Total Fat (kg)	23.4±11.4	21.1±11.3
TBW (L)	36.0±6.7	37.3±8.3
LTM (kg)	43.7±10.7	45.0±11.0
BCM (kg)	25.3±7.2	26.1 ±7.4
Kt/V	1.68±0.60	1.46±0.33
CRP (mg/dL)	3.7±5.6	0.8±0.5
HCT	34.7±4.0	34.2±3.2
Hb(g/dL)	11.2±1.3	10.8±1.0
Iron(μg/dL)	58.2±30.8	51.7±27.2
Ferritin (ng/mL)	1377.3±1170.4	754.3±518.7

All data are mean ± SD. BMI, Body mass index; TBW, Total Body Water; LTM, Lean Tissue Mass; BCM; Body Cell Mass; Kt/V, dialysis efficiency; CRP, C Reactive Protein; HCT, hematocrit; Hb, hemoglobin.

Heart Rate Variability indices are presented in Table 2. Differences were observed for the variables LF and HF pre and 9 month after intradialytic exercise. Also, pNN50% was lower pre exercise program compare with the score of this variable after 9 months of exercise program. Differences were observed finally between hours pre exercise for the variable MEAN RR INTERVAL.

Table 2. Hert Rate Variability indices before and after nine months of intradialytic exercise training

		Pre HD	**1**	**2**	**3**	**4**	**end of HD**
SDNN(ms)	Pre	64.03±44.1	74.5±32.2	58.8±32.9	55.1±35.1	53.8±30.9	52.5±31.5
	9 months later	48.4±19.8	55.7±22.9	62.9±35.2	63.8±38.4	96.7±79.6	164.8±241.0
MEAN RR INTERVAL (ms)	Pre	***838.6±93.3**	800.1±103.6	**763.23±121.4**	711.0±154.5	730.4±156.1	718.7±155.6
	9 months later	802.7±70.8	805.9±79.6	811.3±96.9	807.4±88.0	805.3±99.3	799.8±103.7
LF (ms^2)	Pre	**#67.2±16.5**	68.0±12.9	69.2±10.8	68.4±18.6	67.6±22.8	71.3±22.6
	9 months later	**58.9±20.1**	67.8±17.5	67.2±70.7	67.2±16.4	62.2±17.3	66.1±25.2
HF (ms^2)	Pre	**#32.8±16.5**	32.1±12.9	30.8±10.8	31.6±18.6	32.4±22.8	28.7±22.6
	9 months later	**41.1±20.1**	32.2±17.5	32.8±16.4	32.8±16.4	37.8±17.3	33.9±25.2
LF/HF ratio	Pre	2.7±1.5	2.7±1.5	2.7±1.5	3.5±2.7	3.6±2.6	5.2±5.2
	9 months later	2.1±1.7	2.9±1.8	2.9±2.4	5.3±7.0	2.2±1.3	8.2±17.6
rMSSD(ms)	Pre	42.7±67.2	32.0±23.3	24.0±12.1	20.5±17.5	31.8±37.3	28.8±31.1
	9 months later	31.1±17.2	42.6±34.3	52.3±56.9	49.7±58.8	76.7±102.2	79.8±79.7
pNN50%	Pre	7.7±11.4	**#5.8±4.3**	4.5±3.9	6.6±12.3	9.1±14.8	8.1±12.1
	9 months later	10.3±13.2	**6.3±7.4**	10.0±15.1	10.0±15.1	10.3±15.8	9.5±13.7

All data are mean ± SD.SDNN; standard deviation of the normal RR intervals, MEAN RR INTERVAL; mean duration of all normal to normal RR intervals, LF; low frequency component, HF; high frequency component, rMSSD;square root ofmean squared forward differences of successive NN intervals, pNNS0;proportion of successive NN intervals differences>50

**Differences between hours; # Differences between pre and post exercise*

Echocardiographic data are presented in Table 3.

IVSTd (p=0.029) and DT (p=0.004) obtained before the initialization of the HD session were both found to be significantly lower 9-months after exercise training. Significant improvements were observed in the EF after intradialytic exercise both at baseline and after the nine month intervention period, whilst the pre-HD value of EF appear to be significant improved at baseline after the nine months of exercise training compared to the baseline value (p=0.046). Conventional Doppler as TDI indices of diastolic function did not differ significantly between the two groups (p>0.05). Finally, at the end of hemodialysis session were observed differences in EF% (p= 0.054) and DT (p=0.014).

Table 3. Echocardiographic indices pre and post exercise training

Parameter	Scenario	Pre	During	Post
Standard echocardiographic indices				
IVSTd(mm)	Pre	***11.9±2.2**	11.1±2.3	10.4±1.8
	Post	***9.9±2.3**	11.0±4.2	9.9±2.5
LVPWTd (mm)	Pre	11.0±2.4	10.4±2.4	9.9±1.8
	Post	9.9±2.4	9.3±2.5	9.8±2.1
LVIDd(mm)	Pre	45.5±4.6	28.8±4.0	44.8±4.5
	Post	48.0±6.2	45.6±5.7	46.9±5.6
LV mass(g)	Pre	57.8±9.0	54.2±10.7	51.7±6.9
	Post	55.4±10.2	56.5±15.9	55.1±10.2
LV mass/BSA(g/m^2)	Pre	31.7±3.8	26.7±10.0	28.2±4.3
	Post	29.7±4.4	30.0±5.8	29.3±5.5
LV mass/height^{27}	Pre	14.7±2.2	12.3±4.8	12.9±2.1
	Post	14.1±2.9	14.0±3.7	13.6±3.1
EF (%)	Pre	***48.7±11.1**	52.8±10.1	***50.0±13.4**
	Post	***58.8±6.5**	60.4±10.1	***56.1±3.4**
Delta change of EF	Pre		6.3±7.2	
	Post		0.4±9.6	
Doppler Mitral inflow indices				
E (mm/s)	Pre	0.8±0.2	0.6±0.13	0.7±0.1
	Post	0.8±0.2	0.6±0.2	0.7±0.2
A (mm/s)	Pre	0.9±0.2	0.8±0.3	0.9±0.3
	Post	0.9±0.3	0.8±0 3	0.8±0.3
E/A	Pre	0.9±0.2	0.9±0.3	1.0±0.4
	Post	1.1±0.4	0.9±0.4	0.9±0.3
DT (ms)	Pre	****250.9±48.0**	255.3±70.2	****261.1±61.9**

	Post	****192.3±41.4**	228.5±43.1	****215.0±50.5**
IVRT(ms)	Pre	62.1±12.4	56.6±12.6	63.8±13.2
	Post	73.4±13.3	69.4±17.8	71.6±14.7
Tissue Doppler myocardial velocities indices				
E' (mm/s)	Pre	0.10±0.0	0.1±0.0	0.1±0.0
	Post	0.1±0.0	0.1±0.0	0.1±0.0
A' (mm/s)	Pre	0.9±0.0	0.1±0.0	0.1±0.0
	Post	0.1±0.0	0.1±0.0	0.1±0.1
E'/A'	Pre	1.0±0.4	0.9±0.5	0.8±0.4
	Post	1.3±1.1	0.8±0.3	1.1±0.7
E/E'	Pre	10.2±3.5	8.1±2.7	10.0±4.1
	Post	8.4±3.4	8.6±3.7	7.5±3.7

All data are mean ± SD.

IVSTd, interventricular septum thickness in diastole; LVPWTd, left ventricular posterior wall thickness in diastole; LVIDd, left ventricular internal diameter in diastole; LV, left ventricle; BSA, body surface area; EF, ejection fraction; E, early diastolic mitral flow velocity; A, late diastolic mitral flow velocity; E/A, ratio of early to late diastolic flow velocity; DT, deceleration time; IVRT, isovolumic relaxation time, E', early mitral annular velocity, A', late mitral annular velocity; E'/A', ratio of early to late mitral annular velocity; E/E', ratio of early mitral flow velocity to early mitral annular velocity.

***Correlation is significant at the 0.01 level (2-tailed).*

**Correlation is significant at the 0.05 level (2-tailed).*

Association between echocardiographic indices and body composition

During the pre-exercise scenario TBW, LTM and BCM correlated positively with LV mass and IVSTd (Table 3).

Moreover, linear regression analyses were conducted to predict LV mass and IVSTD based on TBW. The results indicated that TBW explains 47.8% of the variation in the LV mass and 54% of the variation in IVSTd. TBW was a significant predictor of LV mass as well. The regression equation used were: LVmass = 27.45 + 0.69 * TBW, R2 = .48, F(1, 10) = 8.26, p = .018 and IVSTd =3.76 + 0.74* TBW, R2 = .54, F(1, 10) = 10.57, p = .010.

Table 4. Correlations between Body Composition and Echocardiography indices

	IVSTd(mm)	**LVmass(g)**	**BSA(m^2)**	**LVmass/BSA(g/m^2)**	**IVRT(ms)**
TBW(L)	.491(*)	.491(*)	.697(**)		-.585(*)
LTM(kg)	.587(*)	.477(*)			
FAT(kg)				-.527(*)	
BCM(kg)	.564(*)	.491(*)			

All data are mean ± SD. IVSTd, interventricular septum thickness in diastole; LV, Left Ventricle; BSA, body surface area; IVRT, Isovolumic Relaxation Time;TBW, Total Body Water; LTM, Lean Tissue Mass; BCM; Body Cell Mass.

***Correlation is significant at the 0.01 level (2-tailed).*

**Correlation is significant at the 0.05 level (2-tailed).*

After 9-months of exercise training TBW value was positively correlated with LVPWTd (r=0.535, p= 0.046), and BCM value was negatively correlated with EF% (r= -.580, p= 0.034). (Table 4). Also linear regression analysis was conducted to predict LVPWTd based on TBW. The results indicated that TBW explains 43% of the variation in the LVPWTd. TBW was a significant predictor of LVPWTd. The regression equation was: LVPWTd = 3.49 + 0.66 * TBW, R2 = .43, F (1, 8) = 5.35, p = .054.

Table 5. Correlations between Body Composition and echocardiography indices

	LVPWTd(mm)	**EF%**
TBW(L)	0.535(*)	
		-
BCM(kg)		0.580(*)

All data are mean ± SD. LVPWTd, left ventricular posterior wall thickness in diastole; EF, Ejection Fraction; TBW, Total Body Water; BCM; Body Cell Mass.

**Correlation is significant at the 0.05 level (2-tailed).*

Association between echocardiographic indices and HRV

Significant correlations were observed between HRV variables and echocardiography indices when the assessments were conducted before the start of the HD session. In particular, LF, HF and LF/HF ratio correlated with LVmass/BSA, E/A, E' after 9 months of exercise training program (Table 4).

Table 6. Correlations between echocardiographic indices and HRV pre dialysis session

	Scenario	MEAN RR INTERVAL (ms)	SDNN (ms)	rMSDD (ms)	pNN50%	LF(ms^2)	HF(ms^2)	LF/HF
IVSTd(mm)	Pre							
	Post			0.809(**)	0.758(**)			
LVmass/BSA(g/m^2)	Pre							
	Post			0.492(*)		-0.443(*)	0.443(*)	-0.443(*)
E(mm/s)	Pre		-0.614(*)					
	Post							
E/A	Pre							
	9 Post					0.485(*)	-0.485(*)	0.485(*)
DT (ms)	Pre							
	Post		0.492(*)					
IVRT(ms)	Pre							
	Post	-0.486(*)						
E' (mm/s)	Pre					0.582(*)	0.582(*)	0.582(*)
	Post					0.729(**)	0.729(**)	0.729(**)
E/E'	Pre					-0.545(*)	0.545(*)	-0.545(*)
	Post							

All data are mean ± SD.

IVSTd, interventricular septum thickness in diastole; LV, left ventricle; BSA, body surface area; E, early diastolic mitral flow velocity; E/A, ratio of early to late diastolic flow velocity; DT, deceleration time; IVRT, isovolumic relaxation time, E', early mitral annular velocity; E/E', ratio of early mitral flow velocity to early mitral annular velocity; MEAN RR INTERVAL; mean duration of all normal to normal RR intervals, SDNN; standard deviation of the normal RR intervals, rMSSD; square root of mean squared forward differences of successive NN intervals, pNNS0; proportion of successive NN intervals differences>50; LF; low frequency component, HF; high frequency component

***Correlation is significant at the 0.01 level (2-tailed).*

**Correlation is significant at the 0.05 level (2-tailed).*

In Table 5 the data obtained during the HD session are presented. Significant correlations between HRV indices (LF, HF, LF/HF) and echocardiographic indices pre exercise training program were observed (Table 5).

Table 7. Correlations between echocardiographic indices and HRV during the hemodialysis session

	Scenario	**MEAN RR INTERVAL (ms)**	**rMSDD(ms)**	**LF(ms^2)**	**HF(ms^2)**	**LF/HF ratio**
IVSTd(mm)	Pre			-0.511(*)	0.511(*)	-0.539(*)
	Post					
LVPWTD(mm)	Pre					
	Post	-0.485(*)				
LVIDs(mm)	Pre					
	Post					
LVmass/BSA	Pre			-0.564(*)	0.564(*)	-0.587(*)
	Post					
LVmass/height	Pre			-0.600(*)	0.600(*)	-0.624(**)
	Post					
EF%	Pre					
	Post		0.455(*)			
E(mm/s)	Pre	-0.545(*)				
	Post					
E/A (mm/s)	Pre	-0.673(**)				
	Post					
E' (mm/s)	Pre			0.506(*)	-0.506(*)	0.511(*)
	Post		-0.492(*)			
E/E' (mm/s)	Pre	0.697(**)		-0.514(*)	0.514(*)	-0.537(*)
	Post					

All data are mean ± SD.

IVSTd, interventricular septum thickness in diastole; LVPWTd, left ventricular posterior wall thickness in diastole; LVIDd, left ventricular internal diameter in diastole; LV, left ventricle; BSA, body surface area; EF, ejection fraction; E, early diastolic mitral flow velocity; E/A, ratio of early to late diastolic flow velocity; E', early mitral annular velocity, E/E', ratio of early mitral flow velocity to early mitral annular velocity;MEAN RR INTERVAL; mean duration of all normal to normal RR intervals, rMSSD; square

root of mean squared forward differences of successive NN intervals, LF; low frequency component, HF; high frequency component

***Correlation is significant at the 0.01 level (2-tailed).*

**Correlation is significant at the 0.05 level (2-tailed).*

Post hemodialysis A' correlated negatively with rMSDD (r= -.491, p= 0.036).and pNNS0%(r= -.477, p= 0.042) after the 9 months exercise training program (Table 6).

Table 8. Correlations between echocardiographic indices and HRV after dialysis session

	Scenario	**rMSDD(ms)**	**pNN50%**
A'(mm/s)	Pre		
	Post	-0.491(*)	-0.477(*)

All data are mean ± SD.

A', late mitral annular velocity;rMSSD; square root of mean squared forward differences of successive NN intervals, pNNS0; proportion of successive NN intervals differences>50

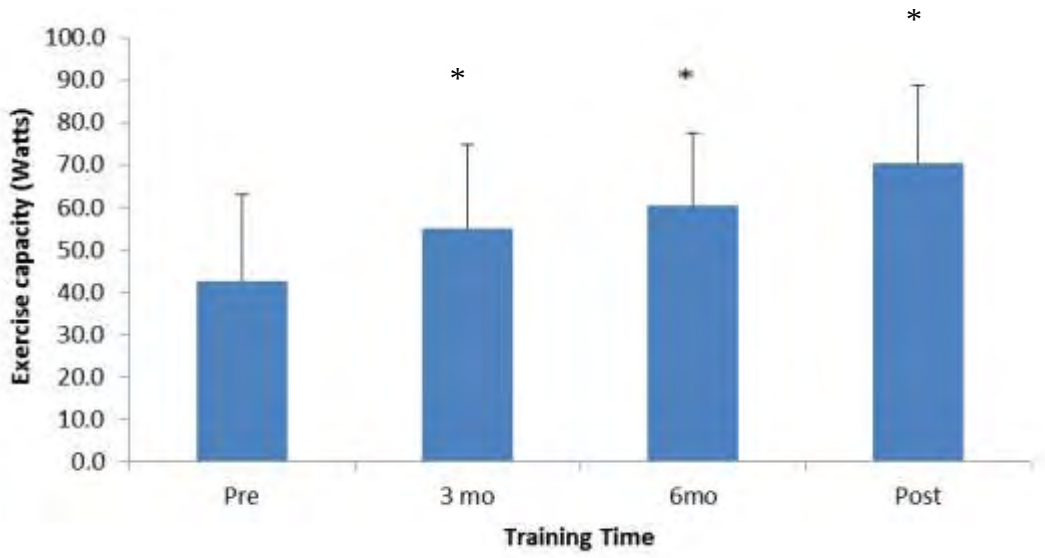


Figure 1. Changes in exercise capacity during the 9-month aerobic exercise training period. * p<0.01 from the pre-training values.

The nine month aerobic exercise intervention improved exercise capacity by 65% (Fig 1)

Functional capacity data are presented in Table 9. All functional tests were improved after the 9 month exercise intervention program with exemption the handgrip where the differences did not reach the statistical significant level (P=0.066) .

Table 9. Functional capacity data before and after the 9 month of exercise training program

	Pre Training	**Post Training**	**P values***
Handgrip	25.8±6.5	28.9±7.4	0.066
STS5(sec)	13.9±5.1	9.2±3.3	**0.005**
STS30(rep)	10.4±2.1	17.3±3.9	**0.000**
STS60(rep)	18.3±5.4	29.8±8.6	**0.000**

*All data are mean ± SD. An unpaired t-test was used to assess the differences between pre and 9 months later of exercise program. STS; sit-to-stand, * Significant changes between Pre and Post values*

Parameters related to fatigue and pain are presented in Table 10. Only the MFI and the FIQ were significantly improved after the implementation of the 9 month intradialytic exercise training.

Table 10. Changes in aspects related to fatigue profile before and after 9 months of intradialytic exercise training

	Pre Training	**Post Training**	**P values***
FSS	3.8±1.2	3.3±1.8	0.510
(0.8-5.2 NV)			
BFI	1.2±1.1	1.4±1.0	0.503
(0-2 NV)			
MFI	50.3±10.1	33.8±15.4	**0.009**
(0-12 NV)			
FIQ	16.2±4.9	7.8±7.1	**0.005**
(0-49 NV)			
PAIN	0.1±0.8	0.1±0.3	0.643
(no clear cut off)			

Abbreviations: FSS, Fatigue Severity Scale; NV; normal values, BFI, Brief Fatigue Inventory; MFI, Multi-Dimensional Fatigue Inventory; FIQ, Fiberomyalgia Impact Questionnaire, PAIN, McGill Pain Questionnaire. Normal values for FSS [236], BFI [237], MFI, FIQ[238]

The associations between echocardiographical indices and functional capacity are presented in Table 11. Left ventricular internal diameter in diastole was strongly correlated with functional capacity and more specific with muscle endurance.

Table 11. Correlations between patients' myocardial stunning indices and functional ability after the 9 months training

	STS30(rep)	**STS60(rep)**
LVIDd	r= -0.605(**)	r=-0.457(*)
	p=0.007	p=0.044

All data are mean ± SD. IVIDd, left ventricular internal diameter in diastole STS, sit-to-stand. * Significant differences at P<0.05, ** Significant differences at P<0.01

Discussion

The aim of this study was to investigate the effect of 9 month exercise training during dialysis on myocardial stunning and HRV in hemodialysis patients. It is well known from previous research that exercise training could result into significant cardioprotective adaptations in HD patients and alleviate the high cardiovascular risk which these patients are exposed to [80] [239].

Myocardial stunning is very common in the HD population and it is associated with increased mortality and morbidity whilst the patients with myocardial stunning tolerate the HD therapy less well compared to the patients who do not exhibit this phenomenon [240]. The present study showed that 9 months of exercise during hemodialysis sessions increased significantly the Ejection Fraction, an index of systolic function of the heart reducing therefore the level of myocardial stunning induced by the hemodialysis therapy. The findings of the current study confirm data derived from previous studies suggested that chronic intradialytic exercise training could induce favorable changes in ejection fraction and thus cardiac function [192, 241] as well as improved stroke volume and cardiac output [192, 242].

In our study the HF parameter was found to be significantly increased after 9 months of exercise training; however the respective improvements in the respective resting values appeared to be significantly decreased. According to the literature, exercise training can reduce emotional distress and concomitantly improve heart rate variability [123] reducing therefore the susceptibility to arrhythmias [241]. Our findings bears of high clinical significance as reduction in the SDNN, LF, and LF/HF parameters predicted cardiovascular death and more specifically sudden death [103]. Taking all into account, is seems that the intradialytic exercise training induced anti-ischemic and anti-arrhythmic cardio-protective effect could reduce myocardial stunning and improve survival in HD patients.

Bioelectrical impedance method has been used before in chronic kidney disease patients in terms of assessing volume status which in terns could negatively affect cardiac morphology [243]. Regarding the body composition and its association with heart functioning, this study indicated that TBW predicted the LV mass and IVSTd. It is well known that LV mass and left ventricular hypertrophy is considered to be strong predictor of mortality in the HD population [244].The usage of the multi-frequency bioelectrical impedance analysis in terms of predicting LV hypertrophy should be examined in depth in the future in order to extract safer conclusions. Another important finding of the current study is the relation between left ventricular internal diameter in diastole with the functional capacity. This finding is highlighting the

relation between cardiovascular health and exercise fitness supporting further the significance of increased physical activity in the everyday routine of patients with end stage renal diseases.

Conclusions

In conclusion, 9 months of intradialytic exercise have promoted a significant improvement of ejection fraction, reducing myocardial stunning induced by the hemodialysis therapy. Those finding come in match with the data of a number of previous studies which have indicated that HD patients who experience cardiovascular instability during intra-dialytic exercise may benefit from exercise programs in the inter-dialytic interval [245]. Therefore, it seems that regularly intradialytic exercise training could be suggested as a non-pharmacological approach for reducing cardiovascular risk of death in HD patients. Long-term controlled studies are needed to evaluate the benefits of exercise training on clinical outcomes.

Research Paper 5: The effect of a 9 month intradialytic exercise training program on neural function in patients receiving hemodialysis therapy

Abstract

Introduction: Uremic peripheral neuropathy is a very common condition occurring in 60-80% in end stage renal disease patients. The uremic polyneuropathy is a distal, sensorimotor polyneuropathy, characterized by segmental demyelination and remyalination as well as axonal degeneration. Uremic neuropathy is considered as a common reason for developing muscle atrophy in HD patients while clinical and neurophysiological indication of recovery from uremic neuropathy has been seen only after renal.

Evidence from non-renal failure patients show that long term regular exercise training could stop or even reverse neural abnormalities however the mechanism that exercise can induce changes in the neural status is partially understood involving peripheral neural adjustments to the metabolic changes after training.

Aims: The aim of the present study was to assess the relationship between fatigue and neural function in HD patients and whether a 9 month intradialytic exercise training program could alter motor and sensory neural function in patients receiving hemodialysis therapy with no clinical evidence of uremic polyneuropathy.

Methods: Seventeen stable undergoing hemodialysis patients were included in the study (15M/2F, 59±13.7 years). All participants completed a 9-month supervised aerobic exercise training program during HD (3 times weekly). Functional capacity assessed by a battery of tests, while pain levels and fatigue profile were assessed via validated questionnaires, before and after the intervention period. Motor and sensory nerve conduction studies on bilateral median, ulnar, peroneal and tibial nerves as well as F-wave were assessed using a full neurographic EMG system and performed pre and post exercise training program.

Results: After the nine month aerobic exercise training intervention, exercise capacity increased by 65% and functional capacity by an average of 40%.Neurological assessment showed that conduction velocity from Tibial and Peroneal nerves was improved by 3.7% and 4.2% respectively after the 9 month intervention while Tibial F-wave latency and Peroneal and Sural nerve distal latency were significantly improved by 4.2%, 4.9% and 10% respectively. Fatigue and pain was improved after the exercise intervention while fatigue score was positively correlated with conduction velocity and amplitude values.

Conclusions: In conclusion the results of the current study demonstrate that exercise training induces beneficial effects on both sensory and motor neural function improving conduction velocity and F-wave latency. Improvements in neural activity are accompanied by changes in fatigue score and pain related aspects. The parallel improvement in motor nerve conduction velocity and its correlations with functional tests supports the hypothesis that exercises could be beneficial for preventing diseases-induced neuropathies in HD patients.

Introduction

The hemodialysis (HD) procedure maintains end-stage renal disease (ESRD) patients alive but as it cannot substitute for a healthy kidney, it heavily taxes the patient's neurophysiology. With regards to skeletal muscle HD patients demonstrate severe atrophy, fat infiltration, and other abnormalities implying often neurological disturbances [98, 109, 133]. With regards to cardiovascular health, hemodialysis-induced cardiac injury may trigger intradialytic and post-dialytic arrhythmias [198] while with regards to mental and emotional health, HD patients face an uphill struggle with diminished autonomy and quality of life, often reflected in depression [199] as they enter the vicious cycle of inactivity fed fatigue which leads to diminishing functional capacity.

Uremic peripheral neuropathy is a very common condition in ESRD patients occurring in 60-80% of these patients population [246]. The uremic polyneuropathy is a distal, sensorimotor polyneuropathy, characterized by segmental demyelination and remyalination as well as axonal degeneration [247]. The electrophysiological characteristics of uremic neuropathy involve peripheral motor and sensory nerves and may deteriorate with age and HD treatment duration [248, 249]. One of the most sensitive parameter for assessing patients polyneuropathy status is the "F-wave latency" which is also an additional to KT/V parameter for assessing dialysis efficiency [249] since reduced nerve conduction velocity is very frequent in HD patients [250]. Uremic neuropathy is considered as a common reason for developing muscle atrophy in HD patients [133, 250] while clinical and neurophysiological indication of recovery from uremic neuropathy has been seen only after transplantation in the majority of the recipients [251, 252].

Research findings examining the association between peripheral polyneuropathy and health related quality of life have shown that depression due to the HD patient's inability to participate in everyday life's activities is becoming an important factors that affects the overall quality of life of these patients population [253]. Noteworthy, increased levels of fatigue are associated with low levels of quality of life in these patients [15]. Fatigue is a common phenomenon in HD patients, yet it is often unrecognized and undertreated [19]. A significant proportion of these patients need more than 3 hours to recover after dialysis due to the post dialysis fatigue [9]. In addition, physical activity and exercise could reduce

fatigue levels, which it is well known to be one of the major factors that contribute to the low quality of life levels in HD patients [254]. There are many nerve conduction studies investigating HD patients [246] however none of those have used any non-pharmacological intervention to improve neural functionality. In addition, exercise trials have been used to improve health and quality of life in HD patients however apart of one study that used neurological examination as a site measurement [100] there are no studies to investigate whether a regular exercise training program could preserve and improve neural functionality in these patients. It seems that long term regular exercise training could stop or even reverse these abnormalities. Indeed studies in healthy volunteers and patients with diabetic neuropathy have shown that exercise training can improve conduction velocity (CV) [255, 256] and reduce incidence of developing motor and sensory neuropathy in the future [257].

The mechanism that exercise can induce changes in the neural status is not fully understood, however, improvements in sleep [131], fatigue [132], functional capacity [133], cardiovascular physiology [258] and peripheral neural adjustments to the metabolic changes after training [100] could at least partially explain some of the improvement seen in those patients after the exercise training period.

The aim of the present study was to assess the relationship between fatigue and neural function in HD patients and whether a 9 month intradialytic exercise training program could alter motor and sensory neural function in patients receiving hemodialysis therapy with no clinical evidence of uremic polyneuropathy.

Methodology

Ethics Statement

The study was approved by the Human Research and Ethics Committee of the University of Thessaly, and by the bioethics committee of the University General Hospital of Larissa, and the General Hospital of Trikala, Greece. All patients gave their written informed consent prior to study participation.

Study population

Seventy eight patients were assessed for eligibility while only seventeen HD patients (15M/2F, 59±13.7 years) participated in the study (Flow Chart). Patients were recruited from the HD unit of the local hospitals and all testing was performed on site in the hospital.

Inclusion & Exclusion criteria

Inclusion criteria were: dialysis for at least six months or more with adequate dialysis delivery (Kt/V > 1.1), and with stable clinical condition. Exclusion criteria were: patients unable to give informed consent, opportunistic infection in the last 3 months, malignancy or infection requiring intravenous antibiotics within 2 months prior to enrollment, with HIV, or musculoskeletal contraindication to exercise or requirement for systemic anticoagulation, participating or having participated in an investigational drug or medical device study within 30 days or five half-lives, pregnant, breast feed or female of childbearing potential who did not agree to remain abstinent or to use an acceptable contraceptive regimen. Also, patients who were judged to have clinically significant abnormalities upon clinical examination or laboratory testing, or who were unable to adequately cooperate because of personal or family conditions, or those who suffered from a mental disorder that interferes with the diagnosis and/or with the conduct of the study, e.g. schizophrenia, major depression, dementia were excluded from this study.

General Study Design

Patients were assessed before (PRE) and after (POST) the 9-month aerobic exercise training program. Training was implemented during their HD session while the exercise program

was supervised by 2 specialized exercise trainers. Cycle exercise was performed 3 times weekly for 60 minutes each time starting between the first 2hr of HD using an adapted cycle ergometer (Model 881 Monark Rehab Trainer, Varberg, Sweden) at an intensity of 50-60% of the patient's maximal exercise capacity, which was estimated during a previous HD session [145, 146].

During and before release from the HD unit, body mass, systolic and diastolic blood pressures (SBP, DBP) and heart rate (using the RS800CX, Polar Electro Oy, Kempele, Finland) were monitored and recorded. Participants' blood chemistry records were recorded before and at the end of the 9-month study. Participants were assessed in aspects related to neural function, exercise and functional capacity.

HD procedure

The patients underwent the HD therapy (Fresenius 4008B, Oberursel, Germany) 3 times per week with low flux, hollow-fiber dialyzers and bicarbonate buffer. The HD session lasted 4 hours. An enoxaparin dose of 40-60 mg was administered intravenously before the beginning of each HD session. EPO therapy was given after the completion of HD session in order to normalize hemoglobin levels within 11-12 (g/dL).

Anthropometrics and Body composition

The patients' dry weight (ideal weight after removal of excess fluids) was recorded from patients medical record. Together with patients' height it was used to calculate body mass index (BMI).Waist and hip peripheries were measured and the waist to hip ratio (WHR) was calculated. Body composition was assessed using a whole-body multi-frequency bio-impedance spectroscopy system (BCM®, Fresenius Medical Care, Bad Homburg, Germany), to estimate fat mass (FM), lean tissue mass (LTM), total body water (TBW) and body cell mass (BCM) [148]. The body composition measurements were taken immediately before the initiation and after the completion of the HD session and with the participants rested in the

supine position. Electrodes were placed on the wrist of the arm without the arterio-venous fistula as well as on the ipsilateral ankle and connected to the BCM device [149].

Blood Chemistry

Routine monthly laboratory results were recorded including C-reactive protein, ferritin, iron, hematocrit, and hemoglobin. The analyses were performed at the clinical biochemistry lab of the University Hospital of Larissa under standard hospital procedures.

Exercise capacity

Using an incremental cycle ergometer test [146] we assessed exercise capacity before, at 3 months, at 6 months and at the end of the 9-month exercise intervention. Values recorded were used to re-adjust the submaximal training intensity of the intradialytic exercise sessions of this program.

Functional Capacity

The patient's functional ability levels were assessed via two Sit-to-Stand tests from which three scores were recorded (time taken to complete 5 sit-to-stands STS-5, number of repetitions in 30'' STS-30 and number of repetitions in a whole minute, STS-60).

Handgrip strength

Maximum isometric handgrip strength, (HGS), was measured on the non-fistula (dominant) side [147] before, every hour during a dialysis session and 30 minutes after the end of HD using a handgrip dynamometer (Charder MG4800 Medical Handgrip Dynamometer, Charder Electronic Taiwan). The dynamometer was adjusted so that it fit comfortably to subjects palm size. Before data collection, a warm-up – familiarisation session was performed followed by 2 min rest. Subjects were instructed to grip the dynamometer and apply maximum force in response to a voice command. The subjects stood with both arms extended sideways from the body with the dynamometer facing away from the body. Two trials were performed with a

rest period of at least 1 min between trials and the highest HGS value, before and after the HD session, was used in the analyses.

Nerve conduction studies

Motor and sensory nerve conduction studies on bilateral median, ulnar, peroneal and tibial nerves as well as F-wave were assessed using a full neurographic EMG system (Keypoint EMG Medtronic, Skovlunde, Denmark). Assessment took place pre and post exercise intervention in all HD patients.

1. Motor conduction studies

The median and ulnar nerve compound muscle action potentials (CMAPs) were evoked with a 1-cm-diameter cathode, 2 cm distal to the 1-cm-diameter anode, and recorded with 1-cm diameter stainless steel disc electrodes. For median nerve motor conduction studies, the recording electrode was placed over the motor point of the abductor pollicis brevis muscle, at the midpoint of a line drawn from the first metacarpophalangeal joint to the insertion of the tendon of the flexor carpi radialis muscle, and with the reference electrode over the distal interphalangeal joint. The median nerve was stimulated at the wrist 80 mm proximal to the recording electrode and at the antecubital fossa. For ulnar nerve motor conduction studies, the recording electrode was placed over the motor point of the abductor digiti minimi muscle, at the midpoint of a line between the fifth metacarpophalangeal joint and the piriform bone, with the reference electrode over the middle phalanx of digit V. The ulnar nerve was stimulated at the wrist 80 mm proximal to the recording electrode and the elbow.

For the tibial nerve, the CMAP was recorded by the active electrode placed over the middle of the abductor hallucis muscle, and the reference electrode placed over the proximal phalanx of digit I. The nerve was stimulated below the medial malleolus and in the popliteal fossa. For peroneal nerve motor conduction studies, the recording electrode was placed in the middle of the extensor digitorum brevis muscle. The peroneal nerve was stimulated at the ankle, 80 mm proximal to the recording electrode, lateral to the

tendon of tibialis anterior muscle, and below the knee, 20–50 mm distal to the proximal part of the caput fibula.

<u>Parameters</u>

The amplitude of the CMAP was measured from baseline to the negative peak. The duration was measured from the point leaving the baseline to the first negative-to-positive crossing of the baseline. The latency of the CMAP was from the stimulus point to the starting point of the wave, normally at the start of the negative deflection. If the first deflection was in a positive direction at the distal stimulation site, even after careful adjustment of the recording electrode placement, the distal latency (DL) was measured

to the first deflection from the baseline. The area of the CMAP was that which existed under the negative peak. The F wave latency was defined from the shortest F-wave latency of 20 consecutive stimuli minus distal motor latencies.

2. Sensory conduction studies

The bipolar fixed electrodes with the 7-mm-diameter cathode 23 mm distal to the 7-mm-diameter anode mounted on a plastic bar (Medtronic 9013L0361) were used for both recording and stimulating. Median and ulnar sensory nerve action potentials (SNAPs) were obtained orthodromically, stimulating from the index fingers (median nerve) or the little finger (ulnar nerve) and recording at the wrist. Sural SNAPs were elicited antidromically, recording behind the lateral malleolus and stimulating on the dorsal aspect of the calf 140 mm proximal to the recording site. The responses were averaged at least 10 times.

Parameters

The amplitude of the SNAP was measured from the negative peak to a line joining the positive peaks. The duration was the time between the positive peaks. The latency of the SNAP was from the stimulus point to the first positive peak. Sensory nerve conduction velocity (CV) included the distal segment, determined by dividing the wrist-to-electrode distance by the latency of the SNAP. The standard reference values for NCS of the testing laboratory were used. The diagnosis of polyneuropathy was based on the presence of one or more abnormalities in two or more nerves on neurography according to standard criteria.

In Tables 1a and 1b are presented the reference normal values of the examined motor and sensory conduction parameters [259].

Table 1a. Reference values of nerve compound muscle action potentials (CMAPs) parameters [259]

	Motor Conduction	>60 years	Standard Adult Normal Range
	Median		
	Amplitude	4-11	4-18
	Conduction Velocity	48-62	49-70
	Distance	70	70
	Distal Latency	2.8-4.5	2.4-4.4
	Ulnar		
	Amplitude	5-15	6-16
	Conduction Velocity	48-65	49-71
	Distal Latency	2.2-3.8	1.8-3.5
	Distance	70	70
	Peroneal		
	Amplitude	1.5-9	2-12
	Conduction Velocity	35-48	41-57
	Distal Latency	3.4-6.1	3.3-6.1
	Distance	90	90
	Tibial		
	Amplitude	3-20	3-26
	Conduction Velocity	38-66	41-53
	Distal Latency	3.5-6.6	2.7-6.1
	Distance	80	80

Table 1b. Reference values of sensory nerve action potentials (SNAPs) parameters [259].

Sensory Conduction	>60 years	Standard Adult Normal Range
Median		
Amplitude	10-60	>20
Conduction Velocity	49-69	53-73
Distal Latency	2.3-4.3	2.5-3.7
Distance	140	140
Ulnar		
Amplitude	8-75	>10
Conduction Velocity	49-76	53-73
Distal Latency	2.5-4.1	2.4-3.5
Distance	140	140
Sural		
Amplitude	4-35	6-47
Conduction Velocity	40-51	>40
Distal Latency	3.3-5.1	3.2-4.2
Distance	140	140

Vital signs measurements

Systolic and Diastolic Blood pressure, Oxygen saturation (SpO2) and Heart Rate (HR) were measured before, every hour and after the dialysis session. Blood pressure and HR were measured automatic using the HD machines BP system, while SpO2 was assessed using a fingertip monitor (Onyx II, Nonin Medical, Inc. Plymouth, MN USA). Data are presented in Paper 3.

Fatigue

Fatigue was assessed using various questionnaires evaluating different aspects of fatigue (chronic, subacute and acute).

Chronic general fatigue was assessed by Fatigue Severity Scale (FSS) [218]. This questionnaire contains nine statements concerning respondent's fatigue to measure fatigue severity. Additionally, we used the Multidimensional Fatigue Inventory (MFI) [219] which is a 20-item scale designed to evaluate in general the dimensions of general fatigue, physical fatigue, reduced motivation, reduced activity, and mental fatigue. For subacute fatigue, we used the Brief Fatigue Inventory (BFI) [151] which is an instrument that can be administered in a clinical setting to assess the severity of fatigue experienced by patients, as well as its impact on their ability to function over the previous 24h.

Pain perception

Each patient completed the McGill pain questionnaire [260] for assessing acute pain sensation and the Fibromyalgia Impact Questionnaire (FIQ) [157]. The FIQ self-administered questionnaire developed to measure fibromyalgia (FM) patient status, progress and outcomes. The instrument contains 11 questions measuring physical functioning, work

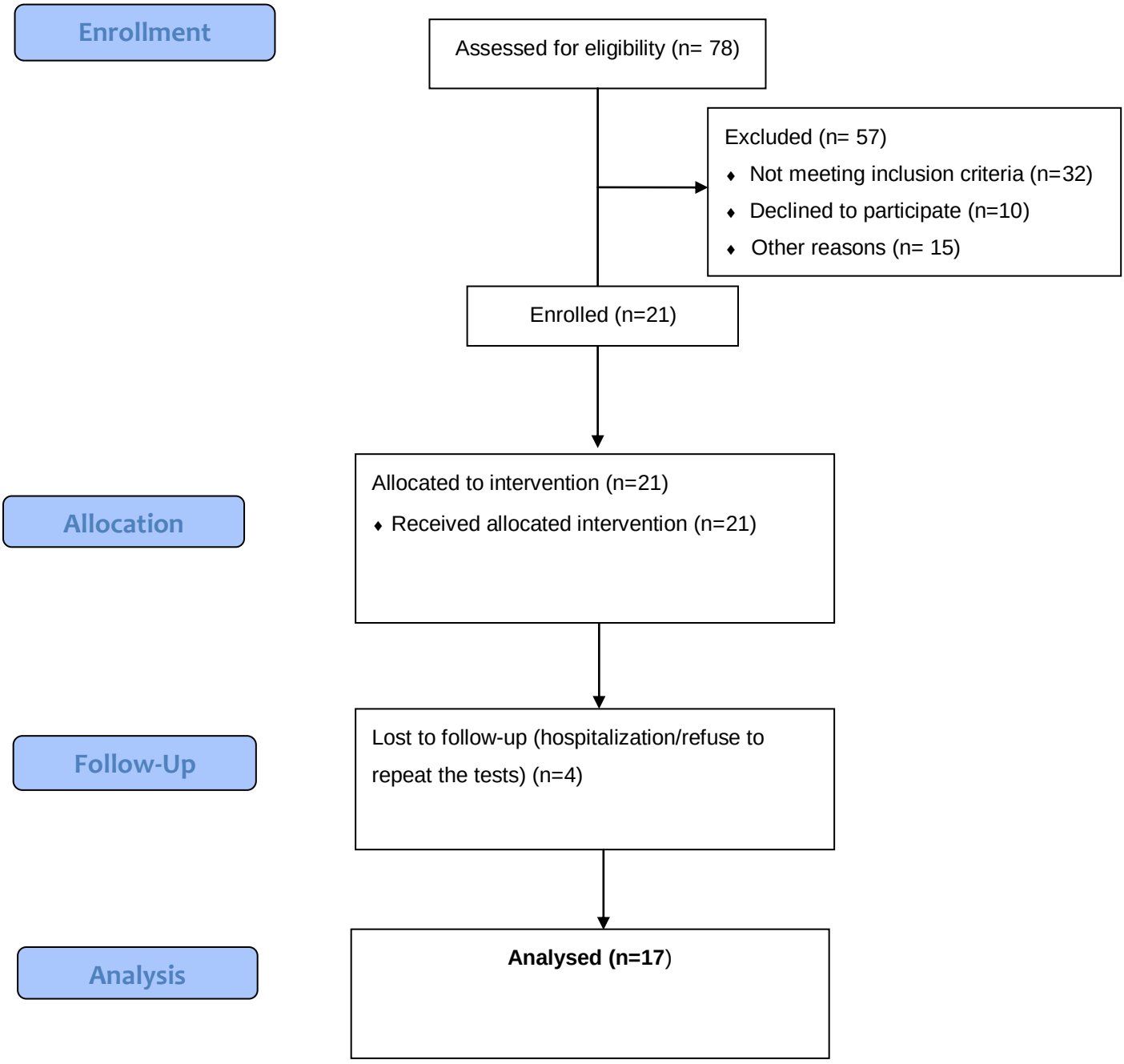
status (missed days of work and job difficulty), depression, anxiety, morning tiredness, pain, stiffness, fatigue, and well-being over the past week.

Statistical analysis

The results are expressed as mean ± SD. Statistical analysis was performed using two-way repeated measures analysis of variance (ANOVA). For comparing initial and final values (pre and post exercise training) paired t test were used for parametric and non-parametric data. All the statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS for Windows, version 18.0, Chicago III). Differences were considered significant when and $P \leq 0.05$.

Results

Flow Chart



Patient basic characteristics are presented in Table 1. All seventeen stable hemodialysis patients who participated in the study completed the 9-month intervention training program without any adverse effects. There were no significant differences between pre and post exercise training program in all baseline variables even though the post training values were numerically improved.

Table 2. Hemodialysis patient basic characteristics

Variables	Pre Training	Post Training
N	17	17
Female/Male	2/15	2/15
Age (yr)	61.3±14.8	61.3±14.8
Weight (kg)	69.8±9.7	70.6±9.2
Height (m)	1.7±0.1	1.7±0.1
BMI (kg/m^2)	24.6±2.6	24.8±2.6
Steps per week	52438.6±26253.3	46749.9±32860.3
Kt/V	1.56±0.46	1.47±0.33
CRP(mg/dL)	2.1±3.9	1.3±3.2
HCT	34.0±3.9	33.3±2.5
Hb(g/dL)	11.0±1.3	10.6±0.8
Iron(μg/dL)	51.8±22.9	57.1±33.5
Ferritin (ng/mL).	525.1±869.1	454.8±503.9
WHR	1.0±0.1	1.0±0.1
Total Fat (kg)	21.5±8.4	19.9±8.2
TBW (L)	34.1±5.6	35.2±6.4
LTM (kg)	41.2±9.3	42.2±9.2
BCM (kg)	23.4±6.2	24.0±6.3

All data are mean ± SD. BMI, Body mass index; CRP, C Reactive Protein; HCT, hematocrit; Hb, hemoglobin; WHR, waist to hip ratio; Kt/V, dialysis efficiency; TBW, total body water; LTM; lean tissue mass; BCM, body cell mass.

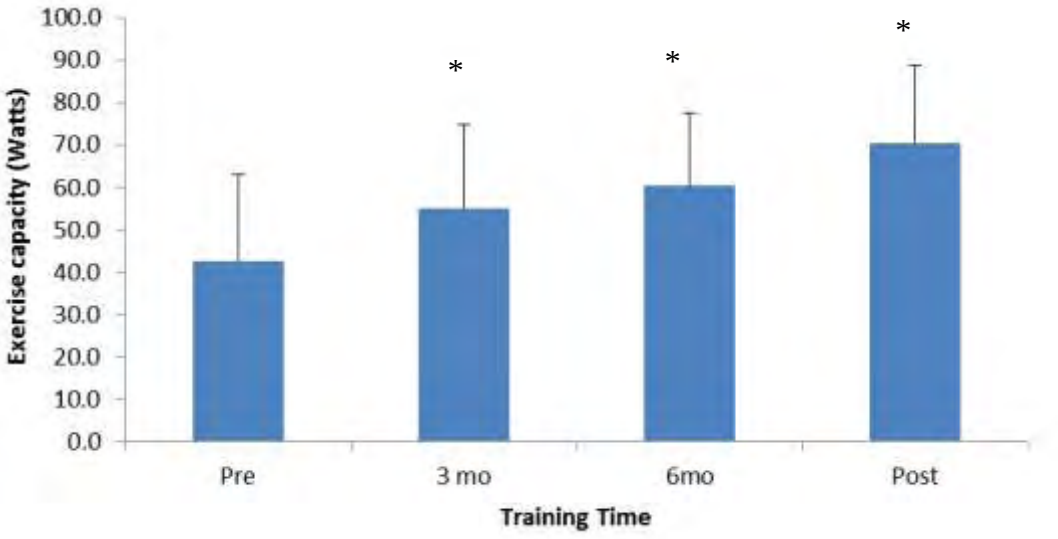


Figure 1. Changes in exercise capacity during the 9-month aerobic exercise training period. * $p<0.01$ from the pre-training values.

None of the patients participated in the study showed signs of peripheral neuropathy. Nine months of intradialytic exercise training program revealed a significant change in the amplitude of the median nerve sensory nerve action potentials (SNAPs) at the end of the intervention period (21.6±10.2) (μV) compared to the initial measurement (12.9±4.5) (μV) (Table 3).

The conduction velocity (CV) of the Tibial nerve was significant different after nine months of exercise training (43.1±3.5) (m/s) compared to pre exercise training values (44.7±4.7) (m/s) while the F wave latency of the same nerve was 55.0±8.3 (ms) and 52.7±6.4 (ms) pre and post training respectively (Table 3).

Analyses indicated a significant prolongation of the peroneal nerve Post exercise (4.1±0.9) (ms) compared to Pre value (3.9±0.6) (ms) while the F wave latency was also significant different Pre and Post exercise training values respectively (45.0±3.4 vs 43.2±4.7) (Table 3).

The exercise training imposed a shortening of sural nerve latency after the 9 months training (Pre 3.0±0.6 vs Post 2.7±0.5) while the amplitude in this nerve was significant increased at

the post training measurements (Pre 10.9±4.5 vs Post 14.0±6.9). All other parameters were essentially unchanged.

Table 3. Nerve conduction assessment pre and post exercise training program

Parameters	Pre Training	Post Training	P values*
Median-M			
L(ms)	3.8±0.6	3.7±0.5	0.121
Amp(mv)	14.4±4.3	13.4±4.6	0.105
CV(m/s)	52.3±5.2	51.4±4.0	0.389
F latency(ms)	29.0±3.2	28.8±2.8	0.616
Median-S			
L(ms)	2.7±0.4	2.7±0.4	0.872
Amp(mv)	12.9±4.5	21.6±10.2	**0.000**
CV(m/s)	52.2±7.4	49.9±5.6	0.328
Ulnar-M			
L(ms)	3.1±0.4	3.0±0.4	0.355
Amp(mv)	13.2±2.8	13.1±3.2	0.815
CV(m/s)	55.4±4.2	55.7±5.6	0.808
F latency(ms)	30.2±3.7	30.0±3.7	0.721
Ulnar-S			
L(ms)	2.4±0.4	2.3±0.3	0.579
Amp(mv)	17.3±8.6	18.3±8.8	0.542
CV(m/s)	51.8±7.4	50.3±6.5	0.630
Tibial			
L(ms)	4.4±0.9	4.9±0.5	0.386
Amp(mv)	14.0±6.2	12.9±6.5	0.174
CV(m/s)	43.1±3.5	44.7±4.7	**0.024**
F latency(ms)	55.0±8.3	52.7±6.4	**0.024**
Peroneal			
L(ms)	4.1±0.9	3.9±0.6	**0.051**
Amp(mv)	6.7±2.8	7.0±3.7	0.534
CV(m/s)	43.2±4.7	45.0±3.4	**0.017**
Sural			
L(ms)	3.0±0.6	2.7±0.5	**0.015**
Amp(mv)	10.9±4.5	14.0±6.9	**0.010**
CV(m/s)	47.9±5.8	47.5±7.3	0.891

*NCS, nerve conduction study; L, latency; Amp, amplitude; CV, conduction velocity; * Significant changes between Pre and Post values*

Data from the assessment of the functional capacity before and after the 9 month intervention are presented in Table 4. Exercise training significantly increased the patient's functional capacity as it was measured via the 3 STS tests. Even though handgrip did not improved statistically, the post values were improved by 5%. STS5, STS30 and STS60 improved by 27%, 39% and 51% respectively.

Table 4. Functional capacity data after 9 months of exercise training program

	Pre Training	**Post Training**	**P values***
Handgrip	27.3±7.3	28.7±6.0	0.394
STS5(sec)	13.6±5.6	9.9±3.5	**0.011**
STS30(rep)	10.1±3.1	14.0±3.3	**0.001**
STS60(rep)	17.1±6.3	25.9±6.4	**0.000**

*All data are mean ± SD. An unpaired t-test was used to assess the differences between pre and 9 months later of exercise program. STS, sit-to-stand, TUG; time up and go; FWT, fast walking test. * Significant changes between Pre and Post values*

Table 5. Changes in aspects related to fatigue profile before and after 9 months of intradialytic exercise training

	Pre Training	**Post Training**	**P values***
FSS	3.6±1.3	3.4±1.4	0.543
(0.8-5.2 NV)			
BFI	1.5±1.3	2.0±1.8	0.367
(0-2 NV)			
MFI	48.1±11.2	41.0±18.4	0.081
(0-12 NV)			
FIQ	15.1±4.8	8.0±6.0	**0.001**
(0-49 NV)			
PAIN	0.1±0.6	0.1±0.5	0.332
(no clear cut off)			

Abbreviations: FSS, Fatigue Severity Scale; NV; normal values, BFI, Brief Fatigue Inventory; MFI, Multi-Dimensional Fatigue Inventory; FIQ, Fiberomyalgia Impact Questionnaire, PAIN, McGill Pain Questionnaire. Normal values for FSS (), BFI (), MFI (), FIQ().

At baseline, significant correlations were observed among nerve conduction parameters and fatigue questionnaires. Fatigue Severity Scale (FSS) negatively correlated with CMAP Peroneal Conduction Velocity (CV) (r=0.353; p< 0.048) while Brief Fatigue Inventory (BFI) positively with the CMAP Tibial amplitude (r=0.409; p<0.023). Mutli-dimensional Fatigue Inventory (MFI) negatively correlated with the Median CMAP F-latency (r=-0.519; p<0.006), Median SNAP Latency (r=-0.366; p<0.046) and with CMAP peroneal Latency (r=-0.457; p< 0.012) and CMAP Tibial F-latency (r=-0.380; p<0.042). Finally Fibromyalgia Impact Questionnaire (FIQ) was negatively associated with SNAP Ulnar Latency (r=-0.379; p<0.038).

After the 9 month exercise training program, MFI positively correlated with Median CMAP Conduction Velocity (CV) **(**r=0.380; p<0.042), SNAP Sural amplitude (r=0.565; p<0.002) and negatively associated with SNAP Sural Latency (r=-0.508; p<0.007). FIQ was positively correlated with Snap Sural Amplitude (r=0.549; p<0.004).

Significant correlations among nerve conduction parameters and functional capacity scores were found. Handgrip correlated with median nerve compound muscle action potentials (CMAPs) latency (r= 0.410; p < 0.027), ulnar CMAP latency (r=0.502; p < 0.008), F wave CMAP latency(r=0.387; p < 0.038), and median SNAP amplitude (r=0.559; p < 0.003). STS30 and STS60 correlated positively with CMAP ulnar latency (r=0.397; p < 0.035), (r=0.412; p < 0.025) respectively. Body composition indices (TBW and LTM) correlated with CMAP median amplitude (r=0.443; p < 0.046), (r=0.485; p < 0.028) respectively.

Table 6. Correlations between patients' neurological assessment, functional ability tests and body composition indices

	Handgrip(NW)	**STS30(rep)**	**STS60(rep)**	**TBW(L)**	**LTM(kg)**
Median-M					
F latency(ms)	r=0.410(*)				
	p=0.027				
Amp(mv)				r= 0.443(*)	r=.485(*)
				p=0.046	p=0.028
Median-S					
Amp(mv)	r=0.559(*)				
	p=0.003				
Ulnar-M					
L(ms)	r=0.502(**)	r=-0.397(*)	r=-0.412(*)		
	p=0.008	p=0.035	p=0.025		
F latency(ms)	r=0.387(*)				
	p=0.038				

Abbreviations: NCS, nerve conduction study; L, latency; Amp, amplitude; CV, conduction velocity; STS, sit-to-stand; TBW, total body water; LTM, lean tissue mass

* Significant differences at P<0.05, ** Significant differences at P<0.01

Discussion

The aim of the present study was to investigate the relationship between fatigue symptoms and neural function in patients receiving HD therapy and whether a 9 month intradialytic exercise training program could alter peripheral nerves' motor and sensory neural functional parameters. This is the first study to show that aerobic exercise training intervention during HD could improve motor and sensory neural function in lower legs nerves and reduce fatigue symptoms in HD patients with no evidence of peripheral neuropathy.

The nine month aerobic exercise intervention improved exercise capacity by 65% (Fig 1) and functional capacity by an average of 40% in agreement with other exercise trials in HD patients where improvement has been ranged between 25 - 145% [61, 146, 212, 261]. The majority of the studies have shown that regular exercise training improves cardiovascular endurance, muscle power and reduce muscle fatigability in CKD patients [262]. Indeed, in our study, muscle fatigue was reduced compared to Pre training values however the differences did not reach the statistical significant level (P=0.06). Pain levels as they assessed by the Fiberomyalgia Impact Questionnaire was significantly improved after the 9 months training even though our patients did not report any significant pain symptoms. This is in agreement with other studies showing the improvement in neural functionality could be accompanied by improvements in pain levels [263].

Peripheral neuropathy is a very common condition in ESRD patients occurring in 60-80% of these patients population [246]. In the current study, none of the examined patients showed any electrophysiological signs or clinical characteristics of peripheral neuropathy probably due to the inclusion criteria applied in the current study that even though did not exclude patients with peripheral neuropathy, all patients had to be capable of participating in the exercise training program and therefore the most capable were self-selected. All nerve conduction studies (NCS) values from Median, Ulnar, Tibial, Peroneal and Sural nerves were within normal aged-matched values. The nine months exercise training showed a beneficial effect in 4 out of 7 peripheral nerves examined (Table 3). Most improved were the lower limb nerves (Tibial, Peroneal and Sural) as it was expected since the aerobic exercise training applied involved only leg (cycling) exercise. More specific, conduction velocity

from Tibial and Peroneal nerves was improved by 3.7% and 4.2% respectively after the 9 month intervention implying that exercise can impose and effective stimuli to increase velocity of action potential propagation in muscle fibers and therefore improved muscle strength and less fatigability [255] something that has been shown in our study (Table 4, Fig 1). Slow conduction velocities often seen in many polyneuropathies and it has been recognized as an early stage characteristic of uremia induced neural deficit with most of the times accompanied by a large F-wave latency [246, 264]. In our study, Tibial F-wave latency and Peroneal and Sural nerve distal latency (DL) were significantly improved after the exercise training program by 4.2%, 4.9% and 10% respectively. Deterioration of neural functionality including prolongation of F-wave latency and slowing of CV has been related to axonal atrophy or breakdown [265], signs that could lead to severe clinical manifestations such as muscle atrophy and weakness [266]. It seems that long term regular exercise training could stop or even reverse these abnormalities. Indeed studies in healthy volunteers have shown that exercise training can improve CV by 3.4% and 6.5% as a result of a concentric or an eccentric isokinetic exercise training [255] while diabetic patients involved in regular exercise training showed 9.4% higher values in Peroneal CV compared to sedentary counterparts [256]. In another study, after a 4yrs follow up, the exercise diabetic patients shown 4% improvements in CV and none incidence of developing motor neuropathy compared to the diabetic control group where 17% of the patients had developed severe motor neuropathy accompanied by 30% of sensory neuropathy [257]. Similar results have been found in studies involved patients with peripheral neuropathies after even a short 10-week supervised exercise training [263]. Until now only one study in HD patients has examined the effect of exercise training in peroneal conduction velocity and distal latency by showing 12.2% and 10.8% improvement respectively while exercise capacity was improved by 29% [100]. In our study, all peripheral nerves have been examined from both upper and lower body with predominant improvements in lower compared to upper limbs. In addition, our findings showed that significant improvements due to exercise training occurred in both sensory and motor nerves from both upper and lower body. This is not unexpected since exercise training very often revitalizes other non-exercising parts of the body including muscles and nerves [267, 268].

Fatigue is one of the most prominent characteristics of the HD patients [12]. In our study, none of the patients had characterized with severe fatigue and most of the scores were within accepted values. The only fatigue questionnaire that showed changes after the 9 months training is the Mutli-dimensional Fatigue Inventory which is one of the best tools for assessing general fatigue. MFI pre training values were negatively correlated with both upper and lower body peripheral nerves values as well as with both sensory and motor type of nerves. Post training, MFI positively correlated with both sensory and motor neural activity while FIQ was positively correlated with SNAP Sural Amplitude. Significant correlations were observed between neural function and functional capacity after the 9 months training (Table 6). More specific handgrip was correlated with both Median and Ulnar nerves while muscle endurance score (STS30, STS60) correlated positively to Ulnar latency. Even though body composition indices (TBW and LTM) did not change significantly after the 9 months training, the post training values correlated with CMAP median amplitude values. This is in agreement with a current theory that hemodialysis fatigue should be seen collectively as a "syndrome" and not in isolation as a sign or symptom induced by another related to renal failure condition [12].

Conclusions

In conclusion the results of the current study demonstrate that exercise training induces beneficial effects on both sensory and motor neural function improving conduction velocity and F-wave latency. Improvements in neural activity are accompanied by changes in of fatigue score and pain related aspects. The parallel improvement in motor nerve conduction velocity and its correlations with functional tests supports the hypothesis that exercises could be beneficial for preventing diseases-induced neuropathies in HD patients.

Discussion

Fatigue is mental, physical and general. Mental fatigue is a psychobiological state caused by prolonged and intensive cognitive activity and is expressed by the lack of concentration and the inability of staying focused under certain conditions [269]. Physical (muscle) fatigue on the other hand is accepted mainly as an inability to exert or sustain muscle force or power output for a given task [270]. Likewise in chronic disease patients, it's been suggested that the symptoms of fatigue relate to two components: the mental that encompasses emotional and cognitive qualities and the physical, encompassing sleepiness, lack of energy and muscle weakness [217].

While hemodialysis *per se* is a lifesaving procedure, it can't substitute for a healthy kidney, it taxes the patient and HD related fatigue symptoms significantly affect patients' quality and way of life as suggested by many [10, 14, 18, 202]. The prevalence of general undefined fatigue in HD patients ranges from 30% to 80% depending on the assessment tools and the dialysis modality [132]. The average score of fatigue in HD patients is the worst of all chronic disease patients [271] including those with severe depression [206], cancer patients undergoing chemotherapy [207] and lupus patients [208]. In addition, the majority of HD patients complain of various "non-specific" symptoms that are very often considered by their health care providers as "irrelevant" to fatigue.

A cause of the observed minimal levels of physical activity is probably that the HD procedure *per se* (e.g. duration of dialysis sessions [202] etc) contributes to fatigue. One third of the patients report that they feel worse in the immediate hours after the dialysis session while one out of four reports severe or very severe intensity of fatigue after dialysis [10]. The severity of "Post-dialysis Fatigue" symptoms could range from mild to severe and can last from a few hours after the dialysis procedure up to until the next day [209] or for a 'very long time' (Gordon et al 2011). Thus many HD patients may spent a large proportion of their time in a state of fatigue [10, 202], and since they perceive fatigue (whether in dialysis or in non-dialysis days) as an important barrier [112], this adversely affects their physical activity levels.

The primary aim of the current PhD research thesis was to investigate the factors involved in the phenomenon called "Hemodialysis Fatigue". The state of current knowledge regarding the differences between generalized fatigue and HD treatment related fatigue is

not well understood however many variables have been implicated in the severity and the prevalence of the symptoms. The etiology of fatigue in HD patients is not a simple "one stop" investigation. It involves many aspects of patients' health as well as various social and behavioral factors that depend on patients' health characteristics and mental attitude [18].

In the current PhD research Thesis we have found that the levels of emotional intelligent are related to the levels of fatigue while patients with low levels of emotional intelligent are more likely to be benefited by an exercise training program compared to medium and high level counterparts. In addition, a single bout of intradialytic exercise did not affect myocardial stunning often observed in hemodialysis patients. Our data support the notion that aerobic exercise training during hemodialysis is a safe and a well tolerable non-pharmacological approach and does not impose any harmful or adverse effect to patients' health or to the hemodialysis therapy per se. This is very reassuring since many health care providers are hesitating to promote exercise in HD patients feeling that will jeopardize patients quality of dialysis and health. After the 9-month aerobic exercise training program all aspects of exercise capacity were improved significantly affecting positively the levels of depression and the cognitive function of the HD patients. One of the most important findings of this thesis is that after the 9 month exercise intervention, the severity and the duration of the Post-Dialysis fatigue symptoms were markedly reduced. It is evident now that exercise training is a very safe and effective non pharmacological approach to ameliorate fatigue symptoms in HD patients either during or after dialysis therapy. Following the improvements in fatigue, a significant improvement in ejection fraction rate by 21% was observed after the exercise training intervention. Intradialytic exercise training can become a complementary tool for improving cardiac functionality and reducing myocardial stunning induced by the hemodialysis therapy. Significant changes were also observed in the nervous system after the 9 months of training. In study 5 we demonstrated that exercise training induces beneficial effects on both sensory and motor neural function improving conduction velocity and F-wave latency. Both indices are considered very reliable in the diagnosis of neuropathies and therefore those findings are of high importance. The improvements in neural activity are accompanied by changes in fatigue score and pain related aspects helping patients to improve quality of life and regain confidence. The parallel improvement in motor nerve conduction velocity and its

correlations with functional tests supports the idea that exercises need to be part of current therapy in every HD patients.

Conclusions

"Fatigue is the inability of sustaining an effort either mentally or physically or both while signs and symptoms may be interconnected in a way not always clearly defined". Fatigue is multifactorial condition that affects many aspects of HD patients' mental and physical health. In the current thesis we have shown that fatigue affects and is affected by emotional, cardiovascular and neurological factors that are not fully understood. It is clear although that exercise training is a safe and low cost non-pharmacological approach that could improve many factors that are involved in the development of "hemodialysis fatigue". Regular exercise training can reduce fatigue symptoms, revitalize cardiovascular and nervous system and significantly improve HD patients' quality of life.

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Appendix

Appendix 1: Bioethics Approval

Εσωτερική Επιτροπή Δεοντολογίας

Τρίκαλα: 10/10/2012

Αριθμ. Πρωτ.: 634

Αίτηση Εξέτασης της πρότασης για διεξαγωγή Έρευνας με τίτλο: Παράμετροι κόπωσης στα χρόνια νοσήματα: η επίδραση της άσκησης και άλλων παρεμβάσεων σε αιμοκαθαιρόμενους ασθενείς.

Επιστημονικώς υπεύθυνος-η / επιβλέπων-ουσα:
Σακκάς Γεώργιος **Ιδιότητα:** Ερευνητής Δ – Διδάσκων
στο ΠΜΣ «Άσκηση & Υγεία» **Ίδρυμα: ΚΕΤΕΑΘ**
Τμήμα: ΙΣΑΑ

Κύριος ερευνητής-τρια / φοιτητής-τρια:ΣΤΕΦΑΝΙΑ ΓΡΗΓΟΡΙΟΥ
Πρόγραμμα Σπουδών: ΠΜΣ «Ψυχολογία της Άσκησης» βασικό πτυχίο στην Ψυχολογία
Ίδρυμα:
ΠΑΝΕΠΙΣΤΗΜΙΟ
ΘΕΣΣΑΛΙΑΣ
Τμήμα: ΤΕΦΑΑ

Η προτεινόμενη έρευνα θα είναι:

Ερευνητικό πρόγραμμα(διδακτορική διατριβή) X Μεταπτυχιακή διατριβή □ Διπλωματική εργασία □

Ανεξάρτητη έρευνα □

Τηλ. επικοινωνίας: 2431-500-911
Email επικοινωνίας: gsakkas@med.uth.gr

Η Εσωτερική Επιτροπή Δεοντολογίας του Τ.Ε.Φ.Α.Α., Πανεπιστημίου Θεσσαλίας μετά την υπ. Αριθμ. 2-3/10-10-2012 συνεδρίασή της εγκρίνει τη διεξαγωγή της προτεινόμενης έρευνας.

Ο Πρόεδρος της Εσωτερικής Επιτροπής Δεοντολογίας – ΤΕΦΑΑ

Τσιόκανος Αθανάσιος
Αναπληρωτής Καθηγητής

Appendix 2: Consent Form

Υπεύθυνη Δήλωση Συμμετοχής

Τίτλος: Η επίδραση της άσκησης κατά την διάρκεια της αιμοκάθαρσης στην κόπωση και ποιότητα ζωής των ασθενών με χρόνια νεφρική ανεπάρκεια.

Αξιότιμοι Κύριοι και Κυρίες,

Το πανεπιστήμιο Θεσσαλίας – ΤΕΦΑΑ & Ιατρική - σε συνεργασία με το Κέντρο Έρευνας Τεχνολογίας και Ανάπτυξης Θεσσαλίας – ΚΕΤΕΑΘ πραγματοποιούν μία ερευνητική μελέτη. Η μελέτη αυτή θα εξετάσει εάν ο συνδυασμός των ντοπαμινεργικών με την άσκηση βελτιώσουν ταχύτερα την φυσική κατάσταση των αιμοκαθερόμενων ασθενών και εάν αυτή η θεραπεία μειώσει τα επίπεδα του καμάτου. Η συμμετοχή σας στην μελέτη είναι προαιρετική και η πιθανή σας άρνηση για συμμετοχή δεν θα τροποποιήσει την ποιότητα της θεραπείας σας. Για την συμμετοχή σας στην μελέτη θα εξετασθείτε από τον θεράποντα Νεφρολόγο που θα δώσει την τελική έγκριση.

Πρωτόκολλο Μελέτης

Για την μελέτη αυτή θα πραγματοποιηθούν διάφορες δοκιμασίες με μια προκαθορισμένη σειρά. Η διάρκεια της μελέτης είναι 9 μήνες. Το πρόγραμμα άσκησης περιλαμβάνει συνεχόμενη ποδηλάτηση μέχρι τα 45 λεπτά κατά την διάρκεια της αιμοκάθαρσης (τρεις φορές την εβδομάδα).

Καμία από αυτές τις εξετάσεις δεν θα σας επιβαρύνει οικονομικά και ούτε θα βάλει σε κάποιο κίνδυνο την υγείας.

Αναλυτικά:

Αιμοληψία

Αμέσως μετά την μελέτη ύπνου, θα σας πάρουμε 25 ml αίμα (περίπου 2 κουταλιές της σούπας) για να εξετάσουμε τα επίπεδα των ορμονών σας στο αίμα αλλά και να εκτιμήσουμε την γενική σας υγεία.

Ερωτηματολόγια

Για την ολοκλήρωση της μελέτης αυτής θα πρέπει να συμπληρώσετε και μια σειρά ερωτηματολογίων που θα μας βοηθήσουν να εκτιμήσουμε την ποιότητα ζωής και του ύπνου σας αλλά και την γενική υγεία σας στην αρχή και μετά από 9 μήνες (με τη λήξη του προγράμματος άσκησης).

Δοκιμασία Φυσικής Δραστηριότητας

Στην εξέταση αυτή θα εκτιμήσουμε την μυϊκή σας αντοχή και δύναμη σε μια σειρά από δοκιμασίες που λάβουν χώρα μέσα στην μονάδα. Αυτές οι δοκιμασίες περιλαμβάνουν:

Δοκιμασία μυϊκής δύναμης (όπου ζητείται από τα άτομα να σφίξουν όσο πιο δυνατά μπορούν για τουλάχιστο 2 sec τη λαβή του χειροδυναμόμετρου κρατώντας μακριά το κορμί τους / πόσες φορές μπορείτε να σηκωθείτε από μια καρέκλα μέσα σε ένα λεπτό. Επίσης θα αξιολογήσουμε μέσω δοκιμασίας βαδίσματος - πόσο γρήγορα μπορείτε να περπατήσετε μια απόσταση 9 μέτρων και μέσω μίας δοκιμασίας βαδίσματος πόσο γρήγορα μπορείτε να περπατήσετε μια απόσταση 3 μέτρων.

Μέτρηση Σωματικής Σύστασης

Η εξέταση μας δίνει πληροφορίες για την σωματική σας σύσταση δηλαδή πόσο από το συνολικό σωματικό σας βάρος είναι σκελετικοί μυς και πόσο είναι λίπος. Η μέτρηση αυτή διαρκεί περίπου 10 λεπτά και είναι ανώδυνη και αναίμακτη.

Κατά την διάρκεια της μέτρησης αυτής θα βρίσκεστε ξαπλωμένη / ος ανάσκελα και ακίνητη / ος για περίπου 10 λεπτά σε ένα αναπαυτικό κρεβάτι καλυμμένοι με ένα σεντόνι. Πάνω από το κρεβάτι θα βρίσκετε μία συσκευή που μοιάζει με κινηματογραφική κάμερα, η οποία θα παίρνει φωτογραφίες το σώμα σας από διάφορες γωνίες. Κατά την διάρκεια της μέτρησης θα πρέπει να μείνετε ακίνητοι. Η εξέταση αυτή θα πραγματοποιηθεί 2 φορές στην αρχή και στο τέλος του 9μηνου προγράμματος.

Νευροφυσιολογικός έλεγχος

Η εξέταση περιλαμβάνει μελέτη της αγωγιμότητας του κινητικού και αισθητικού κλάδου των νεύρων στα άνω άκρα και των νεύρων στα κάτω άκρα.

Ηχοκαρδιογραφία

Η εξέταση περιλαμβάνει υπέρηχους καρδιάς προκειμένου να αξιολογηθούν παράμετροι που σχετίζονται με την καρδιακή λειτουργία και τη συσταλτικότητα (πάχος τοιχώματος, διαμέτρος, κλάσμα εξώθησης, χρόνος επιβράδυνσης κτλ). . Η εξέταση αυτή θα πραγματοποιηθεί 2 φορές στην αρχή και στο τέλος του 9μηνου προγράμματος.

Κίνδυνοι από την μελέτη

Η συμμετοχή σας στην μελέτη αυτή δεν συνιστά κανένα κίνδυνο για την υγεία σας.

Πληροφορίες

Για περισσότερες πληροφορίες απευθυνθείτε στον Δρ. Σακκά στο 2431-500-911 ή στο 6978509102, και στην κα. Γρηγορίου Στεφανία στο 69450-44-917.

Με εκτίμηση

Δρ. Σακκάς Γεώργιος

Η συμμετοχή σας στην μελέτη είναι εθελοντική.

Έχετε το δικαίωμα να αρνηθείτε την συμμετοχή στην μελέτη αυτή ή να αποχωρήσετε ανά πάσα ώρα χωρίς αυτό να αλλάξει την ποιότητα θεραπεία σας στην μονάδα.

<u>Εάν επιθυμείτε να συμμετάσχετε στην μελέτη, παρακαλώ υπογράψτε παρακάτω:</u>

Ονοματεπώνυμο	**Ημερομηνία**	**Υπογραφή**

Μάρτυρας Συμμετοχής

_____

Appendix 3: General Health Questionnaire

Φύλλο ασθενούς (checklist)

ID: _____ Patients Name:_____ Date: _____

Βάρος	
Ύψος	
Περιφέρεια μέσης πυέλου	
ABI	
Ιατρικό ιστορικό	
Στοιχεία αιμοκάθαρσης	
Δείκτης Θρέψης	
Αιματολογικά στοιχεία	
Pills perday	
Neurological Examination	
Cardiological Examination	

Πριν την αιμοκάθαρση

Handgrip			
sıt to stand (5-30-60)			
time up & go (3m)			
fast walking test (6m)			
Bioimpedance			
Αιμοληψία			

Ερωτήσεις οξείας κόπωσης

Ερωτήσεις «Γενικής Κόπωσης»

Αισθάνεσαι έντονη σωματική κούραση τον περισσότερο καιρό?	ΝΑΙ	ΟΧΙ
Αισθάνεσαι ότι η ζωή σου είναι άδεια?	ΝΑΙ	ΟΧΙ
Έχεις έλλειψη συγκέντρωσης – είσαι συχνά αφηρημένος?	ΝΑΙ	ΟΧΙ
Είχες δυσκολία να κοιμηθείς τον τελευταίο μήνα;	ΝΑΙ	ΟΧΙ
Αισθάνθηκες κάποια σωματική αδυναμία τον τελευταίο μήνα?	ΝΑΙ	ΟΧΙ
Αισθάνεσαι γεμάτος ενέργεια?	ΝΑΙ	ΟΧΙ
Πόση ώρα σου παίρνει να συνέλθεις μετά την αιμοκάθαρση;		

Κατά την αιμοκάθαρση

<u>0-60 λεπτά</u>: Γενικά ερωτηματολόγια

1. Mini Mental MMSE	
2. Fatigue Severity Scale (FSS)	
3. Fibromyalgia Impact Questionnaire (FIQ)	
4. SF-36	
5. Zung Depression Scale	
6. Wong Law Emotional Intelligence Scale (WLEIS)	
7. Schutte Self report Emotional Intelligence Scale (SSEIT)	
8. BDI	
9. Missoula Vita Quality of Life	
10. Charlson Comorbidity Index (CCI)	
11. Ερωτηματολόγιο Ημερήσιας Υπνηλίας Epworth	
12. Ποιότητα ύπνου (PSQI) Pittsburgh Sleep Quality Index	
13. Σύνδρομο Ανήσυχων Ποδιών RLS	
14. Malnutrition Inflammation Scale	
15. Ερωτηματολόγιο Πόνου	
16. Multidimensional Fatigue Inventory (MFI)	
17. Brief fatigue Inventory (BFI)	

1η ώρα αιμοκάθαρσης

handgrip	
Αρτηριακή πίεση	
καρδιακή συχνότητα	
κορεσμός αίματος	
Πόσο κουρασμένος αισθάνεσαι ΤΩΡΑ;	
Πόσο ενέργεια νιώθεις ότι έχεις ΤΩΡΑ;	

2η ώρα αιμοκάθαρσης

handgrip	
Αρτηριακή πίεση	
καρδιακή συχνότητα	
κορεσμός αίματος	
Πόσο κουρασμένος αισθάνεσαι ΤΩΡΑ;	

Πόσο ενέργεια νιώθεις ότι έχεις ΤΩΡΑ;	

3η ώρα αιμοκάθαρσης

handgrip	
Αρτηριακή πίεση	
καρδιακή συχνότητα	
κορεσμός αίματος	
Πόσο κουρασμένος αισθάνεσαι ΤΩΡΑ;	
Πόσο ενέργεια νιώθεις ότι έχεις ΤΩΡΑ;	

4η ώρα αιμοκάθαρσης

handgrip	
Αρτηριακή πίεση	
καρδιακή συχνότητα	
κορεσμός αίματος	
Πόσο κουρασμένος αισθάνεσαι ΤΩΡΑ;	
Πόσο ενέργεια νιώθεις ότι έχεις ΤΩΡΑ;	

Αιμοληψία μετά αιμοκαθάρσεως	

Αμέσως μετά την αιμοκάθαρση

Ερωτήσεις καμάτου μετά την αιμοκάθαρση

Πως αισθάνεσαι ΜΕΤΑ την αιμοκάθαρση?	Καλύτερα το ίδιο χειρότερα
Πόσο συχνά βιώνεις έντονη σωματική κούραση ΜΕΤΑ την αιμοκάθαρση?	**0** ποτέ **1** πολύ σπάνια **2** σπάνια **3** περιστασιακά **4** συχνά **5** πολύ συχνά
Πόσο σοβαρή είναι αυτή η κούραση που νιώθεις μετά την αιμοκάθαρση?	**0** καθόλου **1** πολύ ήπια **2** ήπια **3** μέτρια

	4 σοβαρή **5** πολύ σοβαρή
Πόσο διαρκεί αυτή η κούραση που σε πιάνει μετά την αιμοκάθαρση?	**0** καθόλου **1** πολύ λίγο **2** λίγο **3** μέτρια **4** αρκετά **5** πάρα πολύ

Λειτουργικά τεστ

Handgrip			
sıt to stand (5-30-60)			
time up & go (3m)			
fast walking test (6m)			
Bioimpedance			

Appendix 4: Questionnaires

Mini Mental State Exam (MMSE)

1. Προσανατολισμός

Θα σας κάνω μερικές ερωτήσεις για να δούμε πως είναι η μνήμη σας.

- Τι έτος έχουμε;
- Ποια εποχή;
- Τι μήνα;
- Πόσο του μήνα έχουμε;
- Ποια μέρα της εβδομάδας;
- Σε ποια χώρα βρισκόμαστε;
- Σε ποια πόλη;
- Σε ποια περιοχή ή διεύθυνση;
- Σε πιο μέρος βρίσκεστε αυτή τη στιγμή;
- Σε ποιο όροφο;

2. Καταγραφή

Θα σας πω 3 λέξεις που θέλω να επαναλάβετε μετά από μένα και να τις θυμάστε όταν τις ξαναρωτήσω

- Λεμόνι
- Κλειδί
- Μολύβι

3. Συγκέντρωση / Δυνατότητα αριθμητικών πράξεων

Αφαιρέστε από το 100 διαδοχικά 7 μονάδες κάθε φορά / Εναλλακτικά: Γράψτε τη λέξη «πόρτα» ανάποδα

- 93 -α-
- 86 -τ-
- 79 -ρ-
- 72 -ο-
- 65 -π-

4. Ανάκληση

Επαναλάβετε παρακαλώ τις 3 λέξεις που σας είχα ζητήσει προηγουμένως

- Λεμόνι
- Κλειδί
- Μολύβι

5. Κατονομασία

Δείχνουμε στον ασθενή 2 αντικείμενα και ζητούμε να τα κατονομάσει – τι είναι αυτό;

- Ρολόι
- Μολύβι

6. Επανάληψη

Ζητήστε από τον ασθενή να επαναλάβει μετά από σας:

- «Όχι αν και ή αλλά»

7. Εκτέλεση εντολής 3 σταδίων

Δώστε στον ασθενή ένα λευκό φύλλο χαρτί και πείτε του:

- Πάρτε το χαρτί στο δεξί σας χέρι
- Διπλώστε το στη μέση
- Αφήστε το στο πάτωμα

8. Αντίδραση

Δείξτε στον ασθενή ένα χαρτί που να γράφει: «Κλείστε τα μάτια σας»

- Παρακαλώ κάντε ότι γράφει στο χαρτί που σας δείχνω

9. Αυτόματη Γραφή

Δώστε στον ασθενή χαρτί και μολύβι και πείτε:

- Παρακαλώ γράψετε μια ολοκληρωμένη (πρέπει να περιέχει υποκείμενο – ρήμα)

10. Αντιγραφή

- Ζητήστε από τον ασθενή να αντιγράψει ένα σχήμα δύο τεμνόμενων πενταγώνων

Συνολικό άθροισμα MMSE: _____

BRIEF FATIGUE INVENTORY

Κατά τη διάρκεια της ζωής μας οι περισσότεροι από εμάς έχουμε στιγμές όπου νιώθουμε πολύ εξαντλημένοι ή κουρασμένοι. Έχετε αισθανθεί ασυνήθιστα κουρασμένοι κατά την τελευταία εβδομάδα;

Ναι ☐ Όχι ☐

1. Παρακαλώ βαθμολογήστε την κούραση σας (κόπωση, εξάντληση) κυκλώνοντας ένα μόνο αριθμό ο οποίος περιγράφει **την κούραση σας ακριβώς ΤΩΡΑ**.

0	1	2	3	4	5	6	7	8	9	10
Καθόλου κούραση										Η χειρότερη που έχεις φανταστεί

2. Παρακαλώ βαθμολογήστε την κούραση σας (κόπωση, εξάντληση) κυκλώνοντας ένα μόνο αριθμό ο οποίος περιγράφει κατά το σύνηθες το επίπεδο **της κούρασης σας κατά τη διάρκεια του τελευταίου 24ωρου**.

0	1	2	3	4	5	6	7	8	9	10
Καθόλου κούραση										Η χειρότερη που έχεις φανταστεί

3. Παρακαλώ βαθμολογήστε την κούραση σας (κόπωση, εξάντληση) κυκλώνοντας ένα μόνο αριθμό ο οποίος περιγράφει **το χειρότερο επίπεδο της κούρασης (που έχετε νιώσει) κατά τη διάρκεια του τελευταίου 24ωρου**.

0	1	2	3	4	5	6	7	8	9	10
Καθόλου κούραση										Η χειρότερη που έχεις φανταστεί

4. Κυκλώστε ένα μόνο αριθμό ο οποίος περιγράφει πως, κατά τη **διάρκεια του τελευταίου 24ωρου**, ή κούραση σας παρεμβαίνει στη:

Α. Γενική δραστηριότητα

0	1	2	3	4	5	6	7	8	9	10
Δεν παρεμβαίνει										Παρεμβαίνει εντελώς

Β. Διάθεση

0	1	2	3	4	5	6	7	8	9	10
Δεν παρεμβαίνει										Παρεμβαίνει εντελώς

Γ. Ικανότητα βάδισης

0	1	2	3	4	5	6	7	8	9	10
	Δεν παρεμβαίνει									Παρεμβαίνει εντελώς

Δ. Κανονική εργασία (περιλαμβάνει τόσο την εργασία έξω από το σπίτι αλλά και τις καθημερινές εργασίες)

0	1	2	3	4	5	6	7	8	9	10
	Δεν παρεμβαίνει									Παρεμβαίνει εντελώς

Ε. Σχέσεις με άλλους ανθρώπους

0	1	2	3	4	5	6	7	8	9	10
	Δεν παρεμβαίνει									Παρεμβαίνει εντελώς

Ζ. Απόλαυση της ζωής

0	1	2	3	4	5	6	7	8	9	10
	Δεν παρεμβαίνει									Παρεμβαίνει εντελώς

Πολυδιάστατη Κλίμακα Κόπωσης

MULTIDIMENSIONAL FATGIUE INVENTORY (MFI)

Οδηγίες: Με τη βοήθεια των ακόλουθων δηλώσεων, θα θέλαμε να έχουμε μια ιδέα για το πώς έχετε αισθανθεί τον τελευταίο καιρό. Υπάρχει, για παράδειγμα, η δήλωση

"ΑΙΣΘΑΝΟΜΑΙ ΧΑΛΑΡΟΣ"

Εάν νομίζεις ότι αυτή η δήλωση είναι εντελώς αλήθεια, ότι εσύ έχεις νιώσει χαλαρός τελευταία παρακαλώ βάλε ένα Χ στο ακραίο αριστερό κουτί, όπως το παράδειγμα:

Ναι αυτό είναι αλήθεια						Όχι αυτό δεν είναι αλήθεια

1. Αισθάνομαι σε φόρμα	Ναι αυτό είναι αλήθεια						Όχι αυτό δεν είναι αλήθεια
2. Σωματικά αισθάνομαι ικανός να κάνω λίγα πράγματα	Ναι αυτό είναι αλήθεια						Όχι αυτό δεν είναι αλήθεια
3. Αισθάνομαι πολύ ενεργητικός	Ναι αυτό είναι αλήθεια						Όχι αυτό δεν είναι αλήθεια
4. Αισθάνομαι ότι μπορώ να κάνω τα πάντα	Ναι αυτό είναι αλήθεια						Όχι αυτό δεν είναι αλήθεια
5. Αισθάνομαι κουρασμένος	Ναι αυτό είναι αλήθεια						Όχι αυτό δεν είναι αλήθεια
6. Νομίζω ότι κάνω πολλά μέσα σε μια μέρα	Ναι αυτό είναι αλήθεια						Όχι αυτό δεν είναι αλήθεια
7. Όταν κάνω κάτι, μπορώ να είμαι συγκεντρωμένος και αφοσιωμένος στην εργασία μου	Ναι αυτό είναι αλήθεια						Όχι αυτό δεν είναι αλήθεια
8. Σωματικά, αντέχω πολύ/πολλά	Ναι αυτό είναι αλήθεια						Όχι αυτό δεν είναι αλήθεια
9. Διστάζω να κάνω πράγματα	Ναι αυτό είναι αλήθεια						Όχι αυτό δεν είναι αλήθεια
10. Νομίζω κάνω λίγα πράγματα μέσα στην ημέρα	Ναι αυτό είναι αλήθεια						Όχι αυτό δεν είναι αλήθεια
11. Μπορώ να συγκεντρωθώ Αρκετά	Ναι αυτό είναι αλήθεια						Όχι αυτό δεν είναι αλήθεια

12. Είμαι ξεκούραστος	Ναι αυτό είναι αλήθεια						Όχι αυτό δεν είναι αλήθεια
13. Χρειάζεται πολλή προσπάθεια για να συγκεντρωθώ σε πράγματα	Ναι αυτό είναι αλήθεια						Όχι αυτό δεν είναι αλήθεια
14. Σωματικά αισθάνομαι ότι είμαι σε μία άσχημη κατάσταση	Ναι αυτό είναι αλήθεια						Όχι αυτό δεν είναι αλήθεια
15. Έχω πολλά σχέδια	Ναι αυτό είναι αλήθεια						Όχι αυτό δεν είναι αλήθεια
16. Κουράζομαι εύκολα	Ναι αυτό είναι αλήθεια						Όχι αυτό δεν είναι αλήθεια
17. Κάνω λίγα	Ναι αυτό είναι αλήθεια						Όχι αυτό δεν είναι αλήθεια
18. Αισθάνομαι ότι δεν θέλω να κάνω τίποτα	Ναι αυτό είναι αλήθεια						Όχι αυτό δεν είναι αλήθεια
19. Αφαιρούμαι εύκολα	Ναι αυτό είναι αλήθεια						Όχι αυτό δεν είναι αλήθεια
20. Σωματικά αισθάνομαι ότι είμαι σε άριστη κατάσταση	Ναι αυτό είναι αλήθεια						Όχι αυτό δεν είναι αλήθεια

Ερωτηματολόγιο Επιπτώσεων Ινομυαλγίας

Οδηγίες: Για τις ερωτήσεις 1 έως 11 παρακαλώ κυκλώστε τον αριθμό που περιγράφει καλύτερα πως ήσασταν την προηγούμενη εβδομάδα. Εάν εσείς δεν κάνετε κάποια ενέργεια από τις κάτωθι την προηγούμενη εβδομάδα, διαγράψτε την ερώτηση με μία γραμμή.

	Πάντα	Σχεδόν πάντα	Συχνά	Ποτέ
Ήσουν σε θέση να:				
Κάνεις ψώνια? ……	0	1	2	3
Βάλεις πλυντήριο ρούχων και να τα στεγνώσεις?	0	1	2	3
Ετοιμάσεις τα γεύματά σου ?	0	1	2	3
Πλύνεις πιάτα/μαγειρικά σκεύη με τα χέρια?.....	0	1	2	3
Χρησιμοποιήσεις ηλεκτρική σκούπα ?.....	0	1	2	3
Στρώσεις το κρεβάτι σου?	0	1	2	3
Περπατήσεις μερικά τετράγωνα?	0	1	2	3
Επισκεφτείς φίλους ή συγγενείς?	0	1	2	3
Κάνεις δουλειές στην αυλή?.....	0	1	2	3
Οδηγήσεις αμάξι?	0	1	2	3
Ανέβεις σκάλες?	0	1	2	3

12. Από τις 7 ημέρες της προηγούμενης εβδομάδας, πόσες μέρες νιώσατε καλά;

0 1 2 3 4 5 6 7

13. Πόσες ημέρες της προηγούμενης εβδομάδας χάσατε τη δουλειά σας, συμπεριλαμβανομένων και των οικιακών εργασιών εξαιτίας της ινομυαλγίας (έντονου μυϊκού πόνου και καμάτου);

0 1 2 3 4 5 6 7

14. Όταν εσείς εργαστήκατε, πόσο ο πόνος ή άλλα συμπτώματα ινομυαλγίας επηρέασαν την ικανότητά σας για εργασία, συμπεριλαμβανομένων και των οικιακών εργασιών;

Κανένα πρόβλημα με την εργασία •___|___|___|___|___|___|___|___|___|___• Μεγάλη δυσκολία με την εργασία

15. Πόσο άσχημος ήταν ο πόνος σου;

•___|___|___|___|___|___|___|___|___|___•

Καθόλου πόνος Πολύ σοβαρός πόνος

. 16. Πόσο κουρασμένος ήσουν;

•___|___|___|___|___|___|___|___|___|___•

Καθόλου κούραση Πολύ κουρασμένος

. 17. Πώς αισθανόσουν όταν σηκωνόσουν το πρωί;

•___|___|___|___|___|___|___|___|___|___•

Ξύπνησα ξεκούραστος Ξύπνησα πολύ κουρασμένος

. 18. Πόσο άσχημη ήταν η ακαμψία / δυσκαμψία σου;

•___|___|___|___|___|___|___|___|___|___•

Καθόλου ακαμψία Πολύ δύσκαμπτος

. 19. Πόσο νευρικός ή αγχωμένος ένιωσες;

•___|___|___|___|___|___|___|___|___|___•

Καθόλου αγχωμένος Πολύ αγχωμένος

. 20. Πόσο θλιμμένος ή άκεφος έχεις νιώσει;

Καθόλου θλιμμένος Πολύ θλιμμένος

•___| ___|___| ___|___| ___| ___| ___| ___|___•

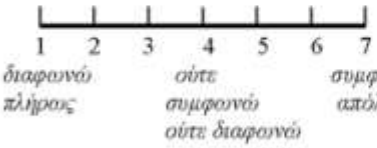
FATIGUE SEVERITY SCALE
[FSS]

Διαβάστε τις παρακάτω δηλώσεις προσεκτικά. Μπορεί να συμφωνείτε ή να διαφωνείτε λίγο ή πολύ με κάθε μία από αυτές.
Σημαδέψτε στην κάθε δήλωση,πάνω στην κλίμακα αξιολόγησης,το σημείο που συμφωνείτε ή διαφωνείτε.
Α)Στο σημείο 1,όταν δεν συμφωνείτε καθόλου με την δήλωση.
Β)Στο σημείο 2 ή 3, άν διαφωνείτε κάπος, αλλά όχι ριζικά.
Γ)Στο σημείο 4, αν δεν μπορείτε ούτε να συμφωνήσετε ούτε να διαφωνήσετε.
Δ)Στο σημείο 5 ή 6 ,αν συμφωνείτε κάπος με τη δήλωση.
Ε)στο σημείο 7,αν συμφωνείτε πλήρως με τη δήλωση

ΔΗΛΩΣΗ	ΚΛΙΜΑΚΑ ΑΞΙΟΛΟΓΗΣΗΣ

1.Η ενεργητικότητα μου μειώνεται όταν είμαι κουρασμένος/η

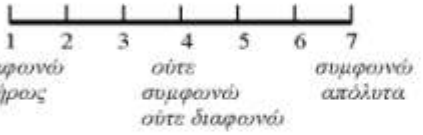
2.Η σωματική άσκηση μου φέρνει κούραση



3.Κουράζομαι εύκολα

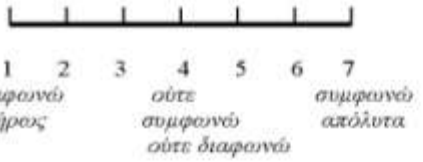
4.Η κούραση παρεμποδίζει τις δραστηριότητές μου

5. Η κούραση μου προκαλεί συχνά προβλήματα

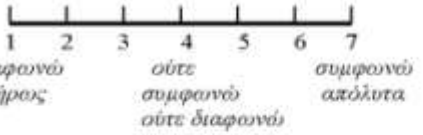


6.Η κούραση δεν μου επιτρέπει παρατεταμένη σωματική δραστηριότητα

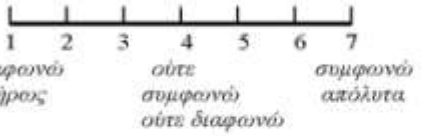
7.Η κούραση με εμποδίζει να εκτελέσω ορισμένα καθήκοντά μου ή να φέρω σε πέρας μερικές υποχρεώσεις μου



8.Η κούραση είναι ένα από τα τρία πιο σοβαρά μου συμπτώματα



9.Η κούραση παρεμποδίζει τη δουλειά μου, την οικογενειακή ή την κοινωνική μου ζωή



ΟΝΟΜΑ..... ΗΛΙΚΙΑ..... ΗΜΕΡ: / /....

ΒΑΘΜΟΛΟΓΙΑ:.....

FSS ©.Προσαρμογή και στάθμιση στα Ελληνικά:
Ζ.Κατσαρού,Σ.Μποσταντζοπούλου και συν., Εγκέφαλος 2007;44:150-157.

SF-36 ΕΡΕΥΝΑ ΥΓΕΙΑΣ

ΟΔΗΓΙΕΣ: Το ερωτηματολόγιο αυτό ζητά τις δικές σας απόψεις για την υγεία σας. Οι πληροφορίες σας θα μας βοηθήσουν να εξακριβώσουμε πώς αισθάνεστε από πλευράς υγείας και πόσο καλά μπορείτε να ασχοληθείτε με τις συνηθισμένες δραστηριότητές σας. Απαντήστε στις ερωτήσεις, βαθμολογώντας κάθε απάντηση με τον τρόπο που σας δείχνουμε. Αν
δεν είστε απόλυτα βέβαιος/βέβαιη για την απάντησή σας, παρακαλούμε να δώσετε την απάντηση που νομίζετε ότι ταιριάζει καλύτερα στην περίπτωσή σας.

1. Γενικά, θα λέγατε ότι η υγεία σας
είναι:(βάλτε έναν κύκλο)

Εξαιρετική 1
Πολύ καλή 2
Καλή 3
Μέτρια 4
Κακή 5

2. Σε σύγκριση με ένα χρόνο πριν, πώς θα αξιολογούσατε την υγεία σας τώρα;
(βάλτε έναν κύκλο)

Πολύ καλύτερη τώρα απ' ότι ένα χρόνο πριν 1
Κάπως καλύτερη τώρα απ' ότι ένα χρόνο πριν 2
Περίπου η ίδια όπως ένα χρόνο πριν 3
Κάπως χειρότερη τώρα απ' ότι ένα χρόνο πριν 4
Πολύ χειρότερη τώρα απ' ότι ένα χρόνο πριν 5

3. Οι παρακάτω προτάσεις περιέχουν δραστηριότητες που πιθανώς να κάνετε κατά τη διάρκεια μιας συνηθισμένης ημέρας. Η τωρινή κατάσταση της υγείας σας, σας περιορίζει σε αυτές τις δραστηριότητες; Εάν ναι, πόσο;

(κυκλώστε έναν αριθμό σε κάθε σειρά)

ΔΡΑΣΤΗΡΙΟΤΗΤΕΣ	Ναι, με περιορίζει Πολύ	Ναι, με περιορίζει Λίγο	Οχι, δεν με περιορίζει Καθόλου
α. Σε κουραστικές δραστηριότητες, όπως το τρέξιμο, το σήκωμα βαριών αντικειμένων, η συμμετοχή σε δυναμικά σπόρ	1	2	3
β. Σε μέτριας έντασης δραστηριότητες, όπως η μετακίνηση ενός τραπεζιού, το σπρώξιμο μιας ηλεκτρικής σκούπας, ο περίπατος στην εξοχή ή όταν παίζετε ρακέτες στην παραλία	1	2	3
γ. Οταν σηκώνετε ή μεταφέρετε ψώνια από την αγορά	1	2	3
δ. Οταν ανεβαίνετε μερικές σκάλες	1	2	3
ε. Οταν ανεβαίνετε μία σκάλα	1	2	3
στ. Στο λύγισμα του σώματος, στο γονάτισμα ή στο σκύψιμο	1	2	3
. Οταν περπατάτε περίπου ένα χιλιόμετρο	1	2	3

η. Οταν περπατάτε μερικές εκατοντάδες μέτρα	1	2	3
θ. Οταν περπατάτε περίπου εκατό μέτρα	1	2	3
ι. Οταν κάνετε μπάνιο ή όταν ντύνεστε	1	2	3

4.Τις τελευταίες 4 εβδομάδες, σας παρουσιάστηκαν - είτε στη δουλειά σας είτε σε κάποια άλλη συνηθισμένη καθημερινή σας δραστηριότητα - κάποια από τα παρακάτω προβλήματα, εξαιτίας της κατάστασης της σωματικής σας υγείας; (κυκλώστε έναν αριθμό σε κάθε σειρά)

	ΝΑΙ	ΟΧΙ
α. Μειώσατε το χρόνο που συνήθως ξοδεύετε στη δουλειά ή σε άλλες δραστηριότητες	1	2
β. Επιτελέσατε λιγότερα από όσα θα θέλατε	1	2
γ. Περιορίσατε τα είδη της δουλειάς ή τα είδη άλλων δραστηριοτήτων σας	1	2
δ. Δυσκολευτήκατε να εκτελέσετε τη δουλειά ή άλλες δραστηριότητές σας (για παράδειγμα, καταβάλατε μεγαλύτερη προσπάθεια)	1	2

5. Τις τελευταίες 4 εβδομάδες, σας παρουσιάστηκαν - είτε στη δουλειά σας είτε σε κάποια άλλη συνηθισμένη καθημερινή δραστηριότητα - κάποια από τα παρακάτω προβλήματα εξαιτίας οποιουδήποτε συναισθηματικού προβλήματος (λ.χ., επειδή νιώσατε μελαγχολία ή άγχος); (κυκλώστε έναν αριθμό σε κάθε σειρά)

	ΝΑΙ	ΟΧΙ
α.Μειώσατε το χρόνο που συνήθως ξοδεύετε στη δουλειά ή σε άλλες δραστηριότητες	1	2
β.Επιτελέσατε λιγότερα από όσα θα θέλατε	1	2
γ.Κάνατε τη δουλειά σας ή και άλλες δραστηριότητες λιγότερο προσεκτικά απ' ότι συνήθως	1	2

6. Τις τελευταίες 4 εβδομάδες, σε ποιο βαθμό επηρέασε η κατάσταση της σωματικής σας υγείας ή κάποια συναισθηματικά προβλήματα τις συνηθισμένες κοινωνικές σας δραστηριότητες με την οικογένεια, τους φίλους, τους γείτονές σας ή με άλλες κοινωνικές ομάδες; (βάλτε έναν κύκλο)

Καθόλου 1
Ελάχιστα 2
Μέτρια 3
Αρκετά 4
Πάρα πολύ 5

7. Πόσο σωματικό πόνο νιώσατε τις τελευταίες 4 εβδομάδες;
(βάλτε έναν κύκλο)

Καθόλου 1
Πολύ ήπιο 2
Ήπιο 3
Μέτριο 4
Εντονο 5
Πολύ έντονο 6

8. Τις τελευταίες 4 εβδομάδες, πόσο επηρέασε ο πόνος τη συνηθισμένη εργασία σας (τόσο την εργασία έξω από το σπίτι όσο και μέσα σε αυτό);
(βάλτε έναν κύκλο)

Καθόλου 1
Λίγο 2
Μέτρια 3
Αρκετά 4
Πάρα πολύ 5

9. Οι παρακάτω ερωτήσεις αναφέρονται στο πώς αισθανόσαστε και στο πώς ήταν γενικά η διάθεσή σας τις τελευταίες 4 εβδομάδες. Για κάθε ερώτηση, παρακαλείστε να δώσετε εκείνη την απάντηση που πλησιάζει περισσότερο σε ό,τι αισθανθήκατε. Τις τελευταίες 4 εβδομάδες, για πόσο χρονικό διάστημα - (κυκλώστε ένα αριθμό σε κάθε σειρά)

	Συνεχώς	Το μεγα-λύτερο διάστημα	Σημαν-τικό διάστημ α	Μερικές φορές	Μικρό διά-στημα	Καθόλου
α. Αισθανόσαστε γεμάτος/γεμάτη ζωντάνια;	1	2	3	4	5	6
β. Είχατε πολύ εκνευρισμό;	1	2	3	4	5	6
γ. Αισθανόσαστε τόσο πολύ πεσμένος/πεσμένη ψυχολογικά, που τίποτε δεν μπορούσε να σας φτιάξει το κέφι;	1	2	3	4	5	6
δ. Αισθανόσαστε ηρεμία και γαλήνη;	1	2	3	4	5	6
ε. Είχατε πολλή ενεργήτικότητα;	1	2	3	4	5	6
στ. Αισθανόσαστε απελπισία και μελαγχολία;	1	2	3	4	5	6
ζ. Αισθανόσαστε εξάντληση;	1	2	3	4	5	6
η. Ησαστε ευτυχισμένος/ ευτυχισμένη;	1	2	3	4	5	6
θ. Αισθανόσαστε κούραση;	1	2	3	4	5	6

10. Τις τελευταίες 4 εβδομάδες, για πόσο χρονικό διάστημα επηρέασαν τις κοινωνικές σας δραστηριότητες (π.χ. επισκέψεις σε φίλους, συγγενείς, κλπ.) η κατάσταση της σωματικής σας υγείας ή κάποια συναισθηματικά προβλήματα;
(βάλτε έναν κύκλο)

Συνεχώς 1
Το μεγαλύτερο διάστημα 2
Μερικές φορές 3
Μικρό διάστημα 4
Καθόλου 5

11. Πόσο αληθίνες η ψευδείς είναι οι παρακάτω προτάσεις στη δική σας περίπτωση;

	Εντελώς Αλήθεια	Μάλλον Αλήθεια	Δεν ξέρω	Μάλλον Ψέμα	Εντελώς Ψέμα
α. Μου φαίνεται ότι αρρωσταίνω λίγο ευκολότερα από άλλους ανθρώπους	1	2	3	4	5
β. Είμαι τόσο υγιής όσο όλοι οι νωστοί μου	1	2	3	4	5
γ. Περιμένω ότι η υγεία μου θα χειροτερεύσει	1	2	3	4	5
δ. Η υγεία μου είναι εξαιρετική	1	2	3	4	5

Κλίμακα Zung **(Zung Self-Rating Depression Scale)**				
Ημερομηνία (ημέρα / μήνας / έτος) **_____/_____/_____** **Patient's ID:_____**	**Παρακαλώ μαρκάρετε με το σήμα (√) την απάντηση που σας αντιπροσωπεύει.**			
Πόσο συχνά αισθάνεστε τα συναισθήματα που αναφέρονται στις παρακάτω προτάσεις;	Σπάνια	Κάποιες φορές	Αρκετές φορές	Τις περισσότερες φορές
1. Αισθάνομαι απογοητευμένος /η και λυπημένος /η				
2. Το πρωί είναι που αισθάνομαι καλύτερα				
3. Νιώθω ότι θέλω να κλάψω, ή κλαίω κάποιες φορές.				
4. Δυσκολεύομαι να κοιμηθώ το βράδυ				
5. Τρώω όπως πάντα				
6. Ακόμα απολαμβάνω το σεξ				
7. Πρόσεξα ότι χάνω βάρος				
8. Έχω προβλήματα δυσκοιλιότητας				
9. Η καρδιά μου χτυπά πιο γρήγορα τον τελευταίο καιρό				

10. Κουράζομαι χωρίς λόγο				

Κλίμακα Zung (συνέχεια) **(Zung Self-Rating Depression Scale)**				
Πόσο συχνά αισθάνεστε τα συναισθήματα που αναφέρονται στις παρακάτω προτάσεις;	Σπάνια	Κάποιες φορές	Αρκετές φορές	Τις περισσότερες φορές
11. Το μυαλό μου είναι καθαρό (χωρίς σκοτούρες) όπως και παλιά				
12. Μου φαίνεται εύκολο να κάνω διάφορα πράγματα όπως παλιά				
13. Είμαι ανήσυχος και δεν μπορώ να καθίσω ήρεμα				
14. Αισθάνομαι αισιόδοξος για το μέλλον				
15. Είμαι πιο δύστροπος/η απ'ότι ήμουνα στο παρελθόν				
16. Μου φαίνεται εύκολο να παίρνω αποφάσεις				
17. Αισθάνομαι ότι είμαι χρήσιμος και αναγκαίος				
18. Έχω μια γεμάτη ζωή				
19. Αισθάνομαι ότι κάποιοι άνθρωποι θα ήταν καλύτερα εάν ήμουν νεκρός				
20. Ακόμα απολαμβάνω τα πράγματα που μου άρεσαν παλιά				

Wang Law Emotional Intelligence (WLEIS)

			Διαφωνώ Απόλυτα	**Συμφωνώ Απόλυτα**
1.	SEA	Τις περισσότερες φορές καταλαβαίνω (έχω μια καλή αίσθηση) του γιατί αισθάνομαι τα συναισθήματα που νοιώθω (έτσι όπως αισθάνομαι).	1..…2…...3…...4…...5…...6…...7	
2.	OAE	Πάντα μπορώ να καταλάβω πως αισθάνονται οι φίλοι μου με βάση την συμπεριφορά τους.	1..…2…...3…...4…...5…...6…...7	
3.	UOE	Πάντα θέτω στόχους για τον εαυτό μου και μετά βάζω τα δυνατά μου για να τους πετύχω.	1..…2…...3…...4…...5…...6…...7	
4.	ROE	Μπορώ με την λογική να ελέγξω τον θυμό μου και να ανταπεξέλθω στις δυσκολίες.	1..…2…...3…...4…...5…...6…...7	
5.	SEA	Έχω μια καλή κατανόηση των συναισθημάτων μου.	1..…2…...3…...4…...5…...6…...7	
6.	OAE	Είμαι καλός παρατηρητής των συναισθημάτων των άλλων	1..…2…...3…...4…...5…...6…...7	
7.	UOE	Πάντα ‘λέω στον εαυτό μου’ ότι είμαι ένα άξιο και ικανό άτομο.	1..…2…...3…...4…...5…...6…...7	
8	ROE	Είμαι απόλυτα ικανός να ελέγξω τα συναισθήματά	1..…2…...3…...4…...5…...6…...7	

		μου	
9..	SEA	Πάντα καταλαβαίνω πώς αισθάνομαι πραγματικά.	1..…2…...3…...4…...5…...6…...7
10.	OAE	Είμαι ευαίσθητος στα συναισθήματα και την συγκινησιακή κατάσταση των άλλων ανθρώπων.	1..…2…...3…...4…...5…...6…...7
11.	UOE	Είμαι ένα άτομο με ισχυρά κίνητρα.	1..…2…...3…...4…...5…...6…...7
12.	ROE	Όταν θυμώνω, πάντα μπορώ να ηρεμήσω γρήγορα.	1..…2…...3…...4…...5…...6…...7
13.	SEA	Πάντα γνωρίζω αν είμαι χαρούμενος ή όχι.	1..…2…...3…...4…...5…...6…...7
14.	OAE	Έχω μια καλή κατανόηση των συναισθημάτων των ανθρώπων γύρω μου	1..…2…...3…...4…...5…...6…...7
15.	UOE	Πάντα παρακινώ τον εαυτό μου να καταφέρει το καλύτερο.	1..…2…...3…...4…...5…...6…...7
16.		Έχω καλό έλεγχο των συναισθημάτων μου.	1..…2…...3…...4…...5…...6…...7

Schutte Self - report Emotional Intelligence Scale (SSEIT)

Προτάσεις	Διαφωνώ Απόλυτα				Συμφωνώ απόλυτα
	1	2	3	4	5
1. Ξέρω πότε είναι η στιγμή να μιλήσω για τα προσωπικά μου προβλήματα σε άλλους.					
2. Όταν αντιμετωπίζω εμπόδια στη ζωή μου, θυμάμαι στιγμές που αντιμετώπισα παρόμοια εμπόδια και τα ξεπέρασα.					
3. Πιστεύω ότι θα τα πάω καλά με τα περισσότερα πράγματα που αναλαμβάνω.					
4. Οι άλλοι άνθρωποι με εμπιστεύονται εύκολα.					
5. Μου είναι δύσκολο να κατανοήσω τα «μη- λεκτικά» νοήματα/ μηνύματα άλλων ανθρώπων . *					
6. Κάποια από τα σημαντικότερα περιστατικά στη ζωή μου με οδήγησαν να επαναπροσδιορίσω τι είναι σημαντικό και τι όχι.					
7. Όταν αλλάζει η διάθεση μου βλέπω νέες δυνατότητες.					
8. Τα συναισθήματα είναι ένα από τα πράγματα που κάνουν την ζωή μου να αξίζει.					
9.Αντιλαμβάνομαι τα συναισθήματα μου καθώς τα βιώνω.					
10. Περιμένω να συμβούν καλά πράγματα.					
11. Μου αρέσει να μοιράζομαι τα συναισθήματα μου με άλλους.					
12. Όταν βιώνω ένα θετικό συναίσθημα, ξέρω πώς να το κάνω να διαρκέσει.					
13. Οργανώνω εκδηλώσεις στις οποίες χαίρονται να συμμετάσχουν άλλοι.					
14. Αναζητώ δραστηριότητες που με κάνουν χαρούμενο/ ή					
15. Αντιλαμβάνομαι τα «μη-λεκτικά» μηνύματα που στέλνω σε άλλους.					
16. Παρουσιάζω τον εαυτό μου με ένα τρόπο που δημιουργεί καλή εντύπωση στους άλλους.					
17. Όταν είμαι ευδιάθετος μου είναι εύκολο να λύνω προβλήματα.					
18. Αναγνωρίζω τα συναισθήματα που βιώνουν οι άλλοι από τις εκφράσεις του προσώπου τους					
19. Γνωρίζω γιατί μεταβάλλονται τα συναισθήματά μου.					
20. Όταν είμαι ευδιάθετος είμαι σε θέση να «επινοώ» νέες ιδέες.					
21. Μπορώ να ελέγχω τα συναισθήματά μου.					
22. Αναγνωρίζω εύκολα τα συναισθήματά					

Ερωτηματολόγιο Κατάθλιψης

Beck Depression Inventory (BDI)

Παρακαλούμε να βάλετε μόνο έναν κύκλο μπροστά στην απάντηση που εκφράζει καλύτερα πως αισθάνεστε. Σημειώστε μία απάντηση από κάθε ενότητα.

Α. 0. Δεν αισθάνομαι λυπημένος
1. Αισθάνομαι λυπημένος ή μελαγχολικός
2α. Είμαι λυπημένος ή μελαγχολικός συνεχώς και δεν μπορώ να απαλλαγώ από αυτό.
2β. Είμαι τόσο μελαγχολικός ή δυστυχισμένος ώστε αυτό μου προξενεί πόνο.
3. Είμαι τόσο μελαγχολικός ή δυστυχισμένος ώστε δεν μπορώ να το αντέξω.

Β. 0. Δεν είμαι ιδιαίτερα απαισιόδοξος ή αποθαρρυμένος για το μέλλον.
1. Αισθάνομαι χωρίς θάρρος για το μέλλον.
2α. Μου φαίνεται ότι δεν έχω τίποτα καλό να περιμένω από το μέλλον
2β. Μου φαίνεται ότι δεν θα ξεπεράσω τις δυσκολίες μου.
3. Μου φαίνεται ότι το μέλλον είναι χωρίς ελπίδα και ότι τα πράγματα δεν μπορεί να φτιάξουν.

Γ. 0. Δεν αισθάνομαι αποτυχημένος.
1. Μου φαίνεται ότι είμαι αποτυχημένος περισσότερο από τους άλλους ανθρώπους
2α. Αισθάνομαι ότι έχω πετύχει στη ζωή μου πολύ λίγα πράγματα άξια λόγου.
2β. Καθώς σκέφτομαι τη ζωή μου μέχρι τώρα το μόνο που βλέπω είναι πολλές αποτυχίες
3. Αισθάνομαι ότι είμαι τελείως αποτυχημένος σαν άτομο (σύζυγος - πατέρας).

Δ. 0. Δεν αισθάνομαι ιδιαίτερα δυσαρεστημένος
1α. Αισθάνομαι βαριεστημένος σχεδόν όλη την ώρα.
1β. Δεν απολαμβάνω τα πράγματα όπως πρώτα.
2. Δεν με ευχαριστεί πια τίποτα.
3. Αισθάνομαι δυσαρεστημένος με το κάθε τι

Ε. 0. Δεν αισθάνομαι ιδιαίτερα ένοχο τον εαυτό μου.
1. Πολλές φορές αισθάνομαι κακός ή χωρίς αξία.
2α. Αισθάνομαι πολύ ένοχος.

2β. Τον τελευταίο καιρό αισθάνομαι κακός ή χωρίς αξία σχεδόν όλη την ώρα.

3. Αισθάνομαι ότι είμαι πολύ κακός ή ανάξιος

Ζ. 0. Δεν αισθάνομαι ότι τιμωρούμαι.

1. Αισθάνομαι ότι κάτι κακό μπορεί να μου συμβεί.

2. Αισθάνομαι ότι τιμωρούμαι ή ότι θα τιμωρηθώ.

3α. Αισθάνομαι ότι μου αξίζει να τιμωρηθώ.

3β. Θέλω να τιμωρηθώ

Παράρτημα ΙΙ

Η. 0. Δεν αισθάνομαι απογοητευμένος από τον εαυτό μου

1α. Αισθάνομαι απογοητευμένος από τον εαυτό μου.

1β. Δεν μου αρέσει ο εαυτός μου.

2. Σιχαίνομαι τον εαυτό μου.

3. Μισώ τον εαυτό μου.

Θ. 0. Δεν αισθάνομαι ότι είμαι χειρότερος από τους άλλους.

1. Είμαι αυστηρός με τον εαυτό μου για τις αδυναμίες μου.

2α. Κατηγορώ τον εαυτό μου για τα λάθη μου.

2β. Κατηγορώ τον εαυτό μου για κάθε κακό που συμβαίνει.

Ι. 0. Δεν μου έρχονται σκέψεις να κάνω κακό στον εαυτό μου.

1. Μου έρχονται σκέψεις να κάνω κακό στον εαυτό μου αλλά ποτέ δεν θα έκανα κάτι τέτοιο.

2α. Μου φαίνεται ότι θα ήταν καλύτερα να πέθαινα.

2β. Μου φαίνεται ότι η οικογένειά μου θα ήταν καλύτερα αν πέθαινα.

2γ. Έχω συγκεκριμένα σχέδια αυτοκτονίας.

3. Θα αυτοκτονούσα αν μπορούσα.

Κ. 0. Δεν κλαίω περισσότερο από το συνηθισμένο.

1. Κλαίω τώρα περισσότερο από ότι συνήθως.

2. Κλαίω συνεχώς, δεν μπορώ να το σταματήσω

3. Άλλοτε μπορούσα να κλάψω, αλλά τώρα μου είναι αδύνατο να κλάψω αν το θέλω.

Λ. 0. Δεν είμαι περισσότερο εκνευρισμένος από ότι συνήθως.

1. Ενοχλούμαι ή εκνευρίζομαι περισσότερο από ότι συνήθως.
2. Αισθάνομαι διαρκώς εκνευρισμένος
3. Δεν εκνευρίζομαι τώρα για πράγματα που με νευρίαζαν συνήθως.

Μ. 0. Δεν έχω χάσει το ενδιαφέρον μου για άλλους ανθρώπους.
1. Ενδιαφέρομαι τώρα λιγότερο για τους άλλους ανθρώπους από ότι παλιότερα.
2. Έχω χάσει το περισσότερο ενδιαφέρον μου για τους άλλους ανθρώπους και τα αισθήματά μου για αυτούς έχουν λιγοστέψει.
3. Έχω χάσει όλο το ενδιαφέρον μου για τους άλλους ανθρώπους και δεν νοιάζομαι καθόλου γι' αυτούς.

Ν. 0. Είμαι το ίδιο αποφασιστικός όπως πάντα.
1. Τελευταία αναβάλλω το να παίρνω αποφάσεις.
2. Έχω μεγάλη δυσκολία στο να παίρνω αποφάσεις.
3. Δεν μπορώ να πάρω καμιά απόφαση.

Ξ. 0. Δεν μου φαίνεται ότι η εμφάνισή μου είναι χειρότερη από άλλοτε.
1. Ανησυχώ μήπως μοιάζω γερασμένος και αντιπαθητικός
2. Αισθάνομαι ότι έγινε τέτοια αλλαγή επάνω μου, ώστε να φαίνομαι αντιπαθητικός
3. Μου φαίνεται ότι είμαι άσχημος και αποκρουστικός

Ο. 0. Τα καταφέρνω στη δουλειά μου όπως και πρώτα.
1α. Χρειάζεται να κάνω ιδιαίτερη προσπάθεια για να αρχίσω κάποια δουλειά.
1β. Δεν τα καταφέρνω στη δουλειά μου όπως πρώτα.
2. Χρειάζεται να πιέσω πολύ τον εαυτό μου για να κάνω κάτι.
3. Μου είναι αδύνατο να εργαστώ.

Π. 0. Κοιμάμαι τόσο καλά όσο συνήθως.
1. Ξυπνώ το πρωί πιο κουρασμένος από άλλοτε.
2. Ξυπνώ το πρωί 2 - 3 ώρες νωρίτερα από άλλοτε και δυσκολεύομαι να ξανακοιμηθώ.
3. Ξυπνώ νωρίς κάθε μέρα και δεν μπορώ να κοιμηθώ πάνω από 5 ώρες το 24ωρο.

Ρ. 0. Δεν κουράζομαι ευκολότερα από ότι συνήθως.
1. Κουράζομαι τώρα ευκολότερα από πρώτα.

2. Κουράζομαι με το παραμικρό που κάνω.

3. Κουράζομαι τόσο εύκολα ώστε δεν μπορώ να κάνω τίποτε.

Σ. 0. Η όρεξή μου δεν είναι χειρότερη από άλλοτε.

1. Η όρεξή μου δεν είναι τόσο καλή όσο άλλοτε.

2. Η όρεξή μου είναι πολύ χειρότερη τώρα.

3. Δεν έχω πια καθόλου όρεξη.

Τ. 0. Δεν έχω χάσει σχεδόν καθόλου βάρος τον τελευταίο καιρό.

1. Έχω χάσει περισσότερο από 2 κιλά.

2. Έχω χάσει περισσότερο από 4 κιλά.

3. Έχω χάσει περισσότερο από 7 κιλά.

Υ. 0. Δεν με απασχολεί η υγεία μου περισσότερο από άλλοτε.

1. Με απασχολούν πόνοι ή βαρυστομαχιά ή δυσκοιλιότητα.

2. Με απασχολεί τόσο πολύ το πως αισθάνομαι ή το τί αισθάνομαι ώστε μου είναι δύσκολο να σκεφτώ τίποτε άλλο.

3. Είμαι εντελώς απορροφημένος με το τι αισθάνομαι.

Φ. 0. Δεν έχω προσέξει τελευταία καμιά αλλαγή στο ενδιαφέρον μου για το σεξ (για τις γυναίκες).

1. Ενδιαφέρομαι τώρα λιγότερο για το σεξ (για τις γυναίκες) από ότι συνήθως.

2. Ενδιαφέρομαι πολύ λιγότερο τώρα για το σεξ (για τις γυναίκες)

3. Έχω χάσει τελείως το ενδιαφέρον μου για το σεξ (για τις γυναίκες)

Missoula - Vitas® Quality Of Life Index

VERSION – 15R

ΟΔΗΓΙΕΣ:

Σημειώστε το βαθμό στον οποίο συμφωνείτε ή διαφωνείτε με τις παρακάτω προτάσεις κυκλώνοντας κάθε φορά μία απάντηση. Αν κάνετε λάθος ή αλλάξετε γνώμη, διαγράψτε με ένα Χ τη λάθος απάντηση και κυκλώστε τη σωστή απάντηση. Παρακαλούμε να απαντήσετε σε όλες τις ερωτήσεις. Σας ευχαριστούμε εκ των προτέρων.

ΣΦΑΙΡΙΚΗ ΠΟΙΟΤΗΤΑ ΖΩΗΣ

Πώς θα βαθμολογούσατε τη συνολική ποιότητα ζωής σας;

1	2	3	4	5
Πολύ φτωχή	Φτωχή	Μέτρια	Καλή	Πολύ καλή

ΣΥΜΠΤΩΜΑΤΑ

1. Αισθάνομαι άρρωστος/η συνέχεια.

-2	-1	0	1	2
Συμφωνώ απόλυτα	Συμφωνώ	Ούτε συμφωνώ ούτε διαφωνώ	Διαφωνώ	Διαφωνώ απόλυτα

2. Είμαι ικανοποιημένος με τον τωρινό έλεγχο των συμπτωμάτων μου.

4	3	0	-3	-4
Συμφωνώ απόλυτα	Συμφωνώ	Ούτε συμφωνώ ούτε διαφωνώ	Διαφωνώ	Διαφωνώ απόλυτα

3. Η σωματική ενόχληση εμποδίζει κάθε ευκαιρία για διασκέδαση.

5	4	3	2	1
Συμφωνώ απόλυτα	Συμφωνώ	Ούτε συμφωνώ ούτε διαφωνώ	Διαφωνώ	Διαφωνώ απόλυτα

ΛΕΙΤΟΥΡΓΙΚΟΤΗΤΑ

4. Δεν είμαι πλέον ικανός/ή να κάνω πολλά από τα πράγματα που μού αρέσει να κάνω.

-2	-1	0	1	2
Συμφωνώ	Συμφωνώ	Ούτε συμφωνώ	Διαφωνώ	Διαφωνώ

απόλυτα ούτε διαφωνώ απόλυτα

5. Αποδέχομαι το γεγονός ότι δεν μπορώ να κάνω πολλά από τα πράγματα που συνήθιζα να κάνω.

4	3	0	-3	-4
Συμφωνώ απόλυτα	Συμφωνώ	Ούτε συμφωνώ ούτε διαφωνώ	Διαφωνώ	Διαφωνώ απόλυτα

6. Η ικανοποίηση από τη ζωή μου εξαρτάται από το να είμαι δραστήριος/α και να μπορώ να αυτοεξυπηρετούμαι.

5	4	3	2	1
Συμφωνώ απόλυτα	Συμφωνώ	Ούτε συμφωνώ ούτε διαφωνώ	Διαφωνώ	Διαφωνώ απόλυτα

ΔΙΑΠΡΟΣΩΠΙΚΕΣ ΣΧΕΣΕΙΣ

7. Τον τελευταίο καιρό είμαι ικανός/ή να μοιράζομαι σημαντικά πράγματα με τα κοντινά μου πρόσωπα.

2	1	0	-1	-2
Συμφωνώ απόλυτα	Συμφωνώ	Ούτε συμφωνώ ούτε διαφωνώ	Διαφωνώ	Διαφωνώ απόλυτα

8. Στην παρούσα φάση περνώ όσο χρόνο θέλω με την οικογένεια και φίλους.

4	3	0	-3	-4
Συμφωνώ απόλυτα	Συμφωνώ	Ούτε συμφωνώ ούτε διαφωνώ	Διαφωνώ	Διαφωνώ απόλυτα

9. Είναι σημαντικό για μένα να έχω στενές προσωπικές σχέσεις.

5	4	3	2	1
Συμφωνώ απόλυτα	Συμφωνώ	Ούτε συμφωνώ ούτε διαφωνώ	Διαφωνώ	Διαφωνώ απόλυτα

ΕΥΕΞΙΑ

10. Οι υποθέσεις μου δεν είναι τακτοποιημένες. Ανησυχώ για το ότι πολλά πράγματα παραμένουν άλυτα.

2	-1	0	1	2
Συμφωνώ απόλυτα	Συμφωνώ	Ούτε συμφωνώ ούτε διαφωνώ	Διαφωνώ	Διαφωνώ απόλυτα

11. Είμαι περισσότερο ικανοποιημένος/η με τον εαυτό μου τώρα από ότι ήμουν πριν την ασθένειά μου.

4	3	0	-3	-4
Συμφωνώ απόλυτα	Συμφωνώ	Ούτε συμφωνώ ούτε διαφωνώ	Διαφωνώ	Διαφωνώ απόλυτα

12. Είναι σημαντικό για μένα να είμαι καλά με τον εαυτό μου.

5	4	3	2	1
Συμφωνώ απόλυτα	Συμφωνώ	Ούτε συμφωνώ ούτε διαφωνώ	Διαφωνώ	Διαφωνώ απόλυτα

<u>ΠΝΕΥΜΑΤΙΚΟΤΗΤΑ</u>

13. Αισθάνομαι ότι η ζωή μου έχει μεγαλύτερο νόημα τώρα από ότι είχε στο παρελθόν.

2	1	0	-1	-2
Συμφωνώ απόλυτα	Συμφωνώ	Ούτε συμφωνώ ούτε διαφωνώ	Διαφωνώ	Διαφωνώ απόλυτα

14. Η ζωή έχει χάσει κάθε αξία για μένα. Η καθημερινότητα είναι ένα βάρος.

-4	-3	0	3	4
Συμφωνώ απόλυτα	Συμφωνώ	Ούτε συμφωνώ ούτε διαφωνώ	Διαφωνώ	Διαφωνώ απόλυτα

15. Είναι σημαντικό για μένα να αισθάνομαι ότι η ζωή μου έχει νόημα.

5	4	3	2	1
Συμφωνώ απόλυτα	Συμφωνώ	Ούτε συμφωνώ ούτε διαφωνώ	Διαφωνώ	Διαφωνώ απόλυτα

Κλίμακα Υπνηλίας Epworth (Epworth Sleepiness Scale)				
Ημερομηνία (ημέρα / μήνας / έτος) _____/_____/_____ Patient's ID:_____	Παρακαλώ κυκλώστε ένα από τα νούμερα που βρίσκονται κάτω από την απάντηση που σας αντιπροσωπεύει.			
Πόσο συχνά νιώθετε υπνηλία (γλαρώνετε) ή σας παίρνει ο ύπνος κατά την διάρκεια των παρακάτω καταστάσεων;	Ποτέ	Μικρή πιθανότητα	Πιθανόν να συμβεί	Σχεδόν πάντα
1. Όταν διαβάζετε ένα βιβλίο ή κάποιο περιοδικό καθισμένος/η	0	1	2	3
2. Όταν βλέπετε τηλεόραση	0	1	2	3
3. Όταν παρακολουθείτε μία συζήτηση σε δημόσιο χώρο ή βλέπετε μια ταινία στον κινηματογράφο	0	1	2	3
4. Όταν ταξιδεύετε σαν συνεπιβάτης σε ένα ΙΧ αυτοκίνητο και δεν έχετε κάνει διάλειμμα για τουλάχιστον μία ώρα	0	1	2	3
5. Όταν ξαπλώνετε το μεσημέρι μετά ρούχα σε έναν καναπέ για να ξεκουρασθείτε	0	1	2	3
6. Όταν κουβεντιάζετε καθιστός	0	1	2	3
7. Όταν μετά το μεσημεριανό σας γεύμα (δεν έχετε καταναλώσει αλκοόλ) καθίσετε και περιμένετε για λίγο	0	1	2	3
8. Όταν οδηγάτε το αυτοκίνητό σας και είστε σταματημένος/η στην κίνηση	0	1	2	3

Δείκτης Ποιότητας Ύπνου του Pittsburgh (**ΔΠΥ**)

Οδηγίες: *Οι ακόλουθες ερωτήσεις σχετίζονται με τις συνήθειες ύπνου τις οποίες είχατε κατά τη διάρκεια μόνον του περασμένου μήνα. Οι απαντήσεις σας θα πρέπει να είναι ακριβείς για την πλειοψηφία των ημερών και νυχτών του περασμένου μήνα. Παρακαλώ, απαντήστε σε όλες τις ερωτήσεις.*

Κατά τη διάρκεια του περασμένου μήνα,

1. Πότε συνήθως πηγαίνατε για ύπνο; _____
2. Πόση ώρα (σε λεπτά) σας έπαιρνε για να κοιμηθείτε, κάθε βράδυ; _____
3. Συνήθως το πρωί τι ώρα ξυπνούσατε; _____
4. Πόσες ώρες κοιμόσασταν πραγματικά κατά τη διάρκεια της νύχτας; (Μη περιλαμβανομένων των ωρών που βρισκόσασταν, άυπνοι στο κρεβάτι; _____

5. Κατά τη διάρκεια του περασμένου μήνα, πόσο συχνά αντιμετωπίσατε προβλήματα ύπνου διότι ……	Όχι κατά τη διάρκεια του περασμένου μήνα (0)	Λιγότερο από 1 φορά την εβδομάδα (1)	Μία ή δύο φορές την εβδομάδα (2)	Τρεις ή περισσότερες φορές την εβδομάδα (3)
α. δεν μπορούσατε να κοιμηθείτε μέσα σε 30 λεπτά;				
β. ξυπνούσατε κατά τα μεσάνυχτα ή πολύ νωρίς το πρωί;				
γ. έπρεπε να σηκωθείτε για τουαλέτα;				
δ. δεν μπορούσατε να αναπνεύσετε ικανοποιητικά;				
ε. είχατε βήχα ή ροχαλίζατε δυνατά;				
στ. κρυώνατε υπερβολικά;				
ζ. ζεσταινόσασταν υπερβολικά;				
η. βλέπατε άσχημα όνειρα;				
θ. πονούσατε;				
ι. ……. άλλες αιτίες. Παρακαλώ περιγράψτε τις αναφέροντας και πόσο συχνά είχατε δυσκολία στον ύπνο λόγω αυτών των αιτιών:				
6. Κατά τη διάρκεια του περασμένου μήνα πόσο συχνά παίρνατε υπνογόνα φάρμακα;				
7. Κατά τη διάρκεια του περασμένου μήνα πόσο συχνά αντιμετωπίσατε πρόβλημα να μείνετε ξύπνιος/α όταν οδηγούσατε, τρώγατε ή σε κάποια κοινωνική δραστηριότητα;				

8. Κατά τη διάρκεια του περασμένου μήνα πόσο δύσκολο σας ήταν να διατηρήσετε τη διάθεσή σας να κάνετε				
	Πολύ καλή (0)	Σχεδόν καλή (1)	Σχεδόν κακή (2)	Κακή
9. Κατά τη διάρκεια του περασμένου μήνα πως θα βαθμολογούσατε την				

ΕΡΩΤΗΜΑΤΟΛΟΓΙΟ ΑΞΙΟΛΟΓΗΣΗΣ ΠΟΝΟΥ

Ημέρα : ____(1 έως 5)

	Καθόλου Πόνος	Ήπιος	Μέτριος	Έντονος
παλμικός-ρυθμικός	**0)**_____	**1)**_____	**2)**_____	**3)**_____
σαν να ‘περπατάει’	**0)**_____	**1)**_____	**2)**_____	**3)**_____
σαν ‘μαχαιριά’	**0)**_____	**1)**_____	**2)**_____	**3)**_____
Οξύς	**0)**_____	**1)**_____	**2)**_____	**3)**_____
σαν ‘κράμπα’	**0)**_____	**1)**_____	**2)**_____	**3)**_____
σαν να ‘δαγκώνει’	**0)**_____	**1)**_____	**2)**_____	**3)**_____
καυστικός – ζεστός	**0)**_____	**1)**_____	**2)**_____	**3)**_____
γενικός – διαρκής	**0)**_____	**1)**_____	**2)**_____	**3)**_____
αίσθημα βάρους	**0)**_____	**1)**_____	**2)**_____	**3)**_____
Ευαίσθητος	**0)**_____	**1)**_____	**2)**_____	**3)**_____
διαμελιστικός-σαν να σε ‘σκίζει’	**0)**_____	**1)**_____	**2)**_____	**3)**_____
Κουραστικός	**0)**_____	**1)**_____	**2)**_____	**3)**_____
αηδιαστικός – νοσηρός	**0)**_____	**1)**_____	**2)**_____	**3)**_____
Τρομακτικός	**0)**_____	**1)**_____	**2)**_____	**3)**_____
βασανιστικός – σκληρός	**0)**_____	**1)**_____	**2)**_____	**3)**_____

ΚΑΘΟΛΟΥ ΠΟΝΟΣ _____ Ο ΧΕΙΡΟΤΕΡΟΣ ΠΟΝΟΣ ΠΟΥ ΕΧΕΤΕ ΝΙΩΣΕΙ ΠΟΤΕ

Ε.Π.Π.

0. Καθόλου Πόνος _____

1. Ήπιος _____

2. Ενοχλητικός _____

3. Οδυνηρός _____

4. Φρικτός _____

5. Αφόρητος _____

Επίπεδα Φυσικής Δραστηριότητας

Ονοματεπώνυμο: _____

Ημερομηνία παραλαβής βηματομετρητή: _____

Αριθμός Βηματομετρητή:_____

No	**Ημερομηνία**	**Βήματα**	**Σχόλια**
1			
2			
3			
4			
5			
6			
7			
	Σύνολο		

Responsibility of: _____

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

Interpretation of the MMSE:

Method	Score	Interpretation
Single Cutoff	<24	Abnormal
Range	<21	Increased odds of dementia
	>25	Decreased odds of dementia
Education	21	Abnormal for 8th grade education
	<23	Abnormal for high school education
	<24	Abnormal for college education
Severity	24-30	No cognitive impairment
	18-23	Mild cognitive impairment
	0-17	Severe cognitive impairment

Interpretation of MMSE Scores:

Score	Degree of Impairment	Formal Psychometric Assessment	Day-to-Day Functioning
25-30	Questionably significant	If clinical signs of cognitive impairment are present, formal assessment of cognition may be valuable.	May have clinically significant but mild deficits. Likely to affect only most demanding activities of daily living.
20-25	Mild	Formal assessment may be helpful to better determine pattern and extent of deficits.	Significant effect. May require some supervision, support and assistance.
10-20	Moderate	Formal assessment may be helpful if there are specific clinical indications.	Clear impairment. May require 24-hour supervision.
0-10	Severe	Patient not likely to be testable.	Marked impairment. Likely to require 24-hour supervision and assistance with ADL.

Source:

- Folstein MF, Folstein SE, McHugh PR: "Mini-mental state: A practical method for grading the cognitive state of patients for the clinician." *J Psychiatr Res* 1975;12:189-198.

Brief Fatigue Inventory

STUDY ID# _____ HOSPITAL # _____

Date: ____/____/____ Time: _____

Name _____ _____ _____

Last First Middle Initial

Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? Yes ☐ No ☐

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.

0 1 2 3 4 5 6 7 8 9 10

No Fatigue — As bad as you can imagine

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10

No Fatigue — As bad as you can imagine

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10

No Fatigue — As bad as you can imagine

4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:

A. General activity

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

C. Walking ability

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

D. Normal work (includes both work outside the home and daily chores)

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

F. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

MFI® MULTIDIMENSIONAL FATIGUE INVENTORY

® E. Smets, B.Garssen, B. Bonke.

Instructions:

By means of the following statements we would like to get an idea of how you have been feeling **lately**. There is, for example, the statement:

"I FEEL RELAXED"

If you think that this is **entirely true**, that indeed you have been feeling relaxed lately, please, place an **X** in the extreme left box; like this:

yes, that is true ☒1 ❑2 ❑3 ❑4 ❑5 no, that is not true

The more you **disagree** with the statement, the more you can place an **X** in the direction of "no, that is not true". Please do not miss out a statement and place only one **X** in a box for each statement.

1	I feel fit.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
2	Physically, I feel only able to do a little.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
3	I feel very active.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
4	I feel like doing all sorts of nice things.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
5	I feel tired.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
6	I think I do a lot in a day.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
7	When I am doing something, I can keep my thoughts on it.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
8	Physically I can take on a lot.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
9	I dread having to do things.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
10	I think I do very little in a day.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
11	I can concentrate well.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
12	I am rested.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
13	It takes a lot of effort to concentrate on things.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
14	Physically I feel I am in a bad condition.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
15	I have a lot of plans.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
16	I tire easily.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
17	I get little done.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
18	I don't feel like doing anything.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
19	My thoughts easily wander.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
20	Physically I feel I am in an excellent condition.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true

FIBROMYALGIA IMPACT QUESTIONNAIRE (FIQ)

Directions: For questions 1 through 11, please circle the number that best describes how you did **overall** for the **past week**. If you don't normally do something that is asked, cross the question out.

	Always	**Most**	**Occasionally**	**Never**
Were you able to:				
1. Do shopping?	0	1	2	3
2. Do laundry with a washer and dryer?	0	1	2	3
3. Prepare meals?	0	1	2	3
4. Wash dishes/cooking utensils by hand?	0	1	2	3
5. Vacuum a rug?.	0	1	2	3
6. Make beds?.	0	1	2	3
7. Walk several blocks?.	0	1	2	3
8. Visit friends or relatives?	0	1	2	3
9. Do yard work?.	0	1	2	3
10.Drive a car?	0	1	2	3
11.Climb stairs?	0	1	2	3

12. Of the 7 days in the past week, how many days did you feel good?

0 1 2 3 4 5 6 7

13. How many days last week did you miss work, including housework, because of fibromyalgia?

0 1 2 3 4 5 6 7

continued on back of page

FIBROMYALGIA IMPACT QUESTIONNAIRE (FIQ)

Directions: For the remaining items, mark the point on the line that best indicates how you felt **overall** for the past week.

14. When you worked, how much did pain or other symptoms of your fibromyalgia interfere with your ability to do your work, including housework?

No problem with work — Great difficulty with work

15. How bad has your pain been?

No pain — Very severe pain

16. How tired have you been?

No tired — Very tiredness

17. How have you felt when you get up in the morning?

Awoke very tired — Awoke well rested

18. How bad has your stiffness been?

No stiff — Very stiffness

19. How nervous or anxious have you felt?

Not anxious

Very anxious

20. How depressed or blue have you felt?

Not depressed

Very depressed

FATIGUE SEVERITY SCALE (FSS)

Date _____ Name _____

Please circle the number between 1 and 7 which you feel best fits the following statements. This refers to your usual way of life within the last week. 1 indicates "strongly disagree" and 7 indicates "strongly agree."

Read and circle a number.	Strongly Disagree → Strongly Agree						
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

VISUAL ANALOGUE FATIGUE SCALE (VAFS)

Please mark an "X" on the number line which describes your global fatigue with 0 being worst and 10 being normal.

0	1	2	3	4	5	6	7	8	9	10

Health Survey for Dialysis Patients (SF36)

Today's Date:_____

Name: Last:_____ First: _____ Date of Birth: _____

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Please answer these questions by "check-marking" your choice. Please select only one choice for each item.

1- In general, would you say your health is:

☐ 1. Excellent ☐ 2. Very good ☐ 3. Good ☐ 4. Fair ☐ 5. Poor

2- Compared to ONE YEAR AGO, how would you rate your health in general NOW?

☐ 1. MUCH BETTER than one year ago.

☐ 2. Somewhat BETTER now than one year ago.

☐ 3. About the SAME as one year ago.

☐ 4. Somewhat WORSE now than one year ago.

☐ 5. MUCH WORSE now than one year ago.

3- The following items are about activities you might do during a typical day. **Does your health now limit you** in these activities? If so, how much?

Activities	**1. Yes, Limited A Lot**	**2. Yes, Limited A Little**	**3. No, Not Limited At All**
a) **Vigorous activities,** such as running, lifting heavy objects, participating in strenuous sports?	☐ 1. Yes, limited a lot	☐ 2. Yes, limited a little	☐ 3. No, not limited at all
b) **Moderate activities,** such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?	☐ 1. Yes, limited a lot	☐ 2. Yes, limited a little	☐ 3. No, not limited at all
c) Lifting or carrying groceries?	☐ 1. Yes, limited a lot	☐ 2. Yes, limited a little	☐ 3. No, not limited at all
d) Climbing **several flights** of stairs?	☐ 1. Yes, limited a lot	☐ 2. Yes, limited a little	☐ 3. No, not limited at all
e) Climbing **one** flight of stairs?	☐ 1. Yes, limited a lot	☐ 2. Yes, limited a little	☐ 3. No, not limited at all
f) Bending, kneeing or stooping?	☐ 1. Yes, limited a lot	☐ 2. Yes, limited a little	☐ 3. No, not limited at all
g) Walking **more than a mile**?	☐ 1. Yes, limited a lot	☐ 2. Yes, limited a little	☐ 3. No, not limited at all
h) Walking **several** blocks?	☐ 1. Yes, limited a lot	☐ 2. Yes, limited a little	☐ 3. No, not limited at all
i) Walking **one** block?	☐ 1. Yes, limited a lot	☐ 2. Yes, limited a little	☐ 3. No, not limited at all
j) Bathing or dressing yourself?	☐ 1. Yes, limited a lot	☐ 2. Yes, limited a little	☐ 3. No, not limited at all

4- During the **past 4 weeks**, have you had any of the following problems with your work or other regular activities *as a result of your physical health*?

	Yes	No
a) Cut down on the **amount of time** you spent on work or other activities?	☐ 1. yes	☐ 2. No
b) **Accomplished less** than you would like?	☐ 1. yes	☐ 2. No
c) Were limited in the **kind** of work or other activities?	☐ 1. yes	☐ 2. No
d) Had **difficulty** performing the work or other activities (for example it took extra effort)?	☐ 1. yes	☐ 2. No

5. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
a) Cut down on the **amount of time** you spent on work or other activities?	1. yes	2. No
b) **Accomplished less** than you would like?	1. yes	2. No
c) Didn't do work or other activities as **carefully** as usual?	1. yes	2. No

6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

1. Not at all 2. Slightly 3. Moderately 4. Quite a bit 5. Extremely

7. How much **bodily pain** have you had during the **past 4 weeks**?

1. None 2. Very mild 3. Mild 4. Moderate 5. Severe 6. Very severe

8. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

1. Not at all 2. A little bit 3. Moderately 4. Quite a bit 5. Extremely

9. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question , please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 week** ...

	1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. None of the time
a) Did you feel full of pep?	☐ 1. All of the time	☐ 2. Most of the time	☐ 3. A good bit of the time	☐ 4. Some of the time	☐ 5. A little of the time	☐ 6. None of the time
b) Have you been a very nervous person?	☐ 1. All of the time	☐ 2. Most of the time	☐ 3. A good bit of the time	☐ 4. Some of the time	☐ 5. A little of the time	☐ 6. None of the time
c) Have you felt so down in the dumps that nothing could cheer you up?	☐ 1. All of the time	☐ 2. Most of the time	☐ 3. A good bit of the time	☐ 4. Some of the time	☐ 5. A little of the time	☐ 6. None of the time
d) Have you felt calm and peaceful?	☐ 1. All of the time	☐ 2. Most of the time	☐ 3. A good bit of the time	☐ 4. Some of the time	☐ 5. A little of the time	☐ 6. None of the time
e) Did you have a lot of energy?	☐ 1. All of the time	☐ 2. Most of the time	☐ 3. A good bit of the time	☐ 4. Some of the time	☐ 5. A little of the time	☐ 6. None of the time
f) Have you felt downhearted and blue?	☐ 1. All of the time	☐ 2. Most of the time	☐ 3. A good bit of the time	☐ 4. Some of the time	☐ 5. A little of the time	☐ 6. None of the time
g) Do you feel worn out?	☐ 1. All of the time	☐ 2. Most of the time	☐ 3. A good bit of the time	☐ 4. Some of the time	☐ 5. A little of the time	☐ 6. None of the time
h) Have you been a happy person?	☐ 1. All of the time	☐ 2. Most of the time	☐ 3. A good bit of the time	☐ 4. Some of the time	☐ 5. A little of the time	☐ 6. None of the time
i) Did you feel tired?	☐ 1. All of the time	☐ 2. Most of the time	☐ 3. A good bit of the time	☐ 4. Some of the time	☐ 5. A little of the time	☐ 6. None of the time

10. During the **past 4 weeks**, how much of the time has your **physical health** or **emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

☐ 1. All of the time

☐ 2. Most of the time.

☐ 3. Some of the time

☐ 4. A little of the time.

☐ 5. None of the time.

11. How TRUE or FALSE is **each** of the following statements for you?

	1. Definitely true	2. Mostly true	3. Don't know	4. Mostly false	5. Definitely false
a) I seem to get sick a little easier than other people?	☐ 1. Definitely true	☐ 2. Mostly true	☐ 3. Don't know	☐ 4. Mostly false	☐ 5. Definitely false
b) I am as healthy as anybody I know?	☐ 1. Definitely true	☐ 2. Mostly true	☐ 3. Don't know	☐ 4. Mostly false	☐ 5. Definitely false
c) I expect my health to get worse?	☐ 1. Definitely true	☐ 2. Mostly true	☐ 3. Don't know	☐ 4. Mostly false	☐ 5. Definitely false
d) My health is excellent?	☐ 1. Definitely true	☐ 2. Mostly true	☐ 3. Don't know	☐ 4. Mostly false	☐ 5. Definitely false

Thank you!

ZUNG SELF-RATING DEPRESSION SCALE

Patient's Initials

Date of Assessment

Please read each statement and decide how much of the time the statement describes how you have been feeling during the past several days.

Make check mark (✓) in appropriate column.	A little of the time	Some of the time	Good part of the time	Most of the time
1. I feel down-hearted and blue				
2. Morning is when I feel the best				
3. I have crying spells or feel like it				
4. I have trouble sleeping at night				
5. I eat as much as I used to				
6. I still enjoy sex				
7. I notice that I am losing weight				
8. I have trouble with constipation				
9. My heart beats faster than usual				
10. I get tired for no reason				
11. My mind is as clear as it used to be				
12. I find it easy to do the things I used to				
13. I am restless and can't keep still				
14. I feel hopeful about the future				
15. I am more irritable than usual				
16. I find it easy to make decisions				
17. I feel that I am useful and needed				
18. My life is pretty full				
19. I feel that others would be better off if I were dead				
20. I still enjoy the things I used to do				

Adapted from Zung, A self-rating depression scale, *Arch Gen Psychiatry*, 1965;12:63-70.

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APPI

Measurement for Emotional Intelligence: Wong's Emotional Intelligence Scale (WEIS)

Please circle the number on the right hand columns to indicate your agreement with the following statements: 1=strongly disagree; 2=disagree; 3=slightly disagree; 4=neither disagree nor agree; 5=slightly agree; 6=agree; 7=strongly agree							
1. I have a good sense of why I have certain feelings most of the time.	1	2	3	4	5	6	7
2. I have good understanding of my own emotions.							
3. I really understand what I feel.							
4. I always know whether or not I am happy.							
5. I am able to control my temper so that I can handle difficulties rationally.							
6. I am quite capable of controlling my own emotions.							
7. I can always calm down quickly when I am very angry.							
8. I have good control of my own emotions.							
9. I always set goals for myself and then try my best to achieve them.							
10. I always tell myself I am a competent person.							
11. I am a self-motivating person.							
12. I would always encourage myself to try my best.							
13. I always know my friends' emotions.							
14. I am a good observer of others' emotions.							
15. I am sensitive to the feelings and emotions of others.							
16. I have good understanding of the emotions of people around me.							

The 33-item emotional intelligence scale

(1) I know when to speak about my personal problems to others
(2) When I am faced with obstacles, I remember times I faced similar obstacles and overcame them
(3) I expect that I will do well on most things I try
(4) Other people find it easy to confide in me
(5) I find it hard to understand the non-verbal messages of other people*
(6) Some of the major events of my life have led me to re-evaluate what is important and not important
(7) When my mood changes, I see new possibilities
(8) Emotions are one of the things that make my life worth living
(9) I am aware of my emotions as I experience them
(10) I expect good things to happen
(11) I like to share my emotions with others
(12) When I experience a positive emotion, I know how to make it last
(13) I arrange events others enjoy
(14) I seek out activities that make me happy
(15) I am aware of the non-verbal messages I send to others
(16) I present myself in a way that makes a good impression on others
(17) When I am in a positive mood, solving problems is easy for me
(18) By looking at their facial expressions, I recognize the emotions people are experiencing
(19) I know why my emotions change
(20) When I am in a positive mood, I am able to come up with new ideas
(21) I have control over my emotions
(22) I easily recognize my emotions as I experience them
(23) I motivate myself by imagining a good outcome to tasks I take on
(24) I compliment others when they have done something well
(25) I am aware of the non-verbal messages other people send
(26) When another person tells me about an important event in his or her life, I almost feel as though I have experienced this event myself
(27) When I feel a change in emotions, I tend to come up with new ideas
(28) When I am faced with a challenge, I give up because I believe I will fail*
(29) I know what other people are feeling just by looking at them
(30) I help other people feel better when they are down
(31) I use good moods to help myself keep trying in the face of obstacles
(32) I can tell how people are feeling by listening to the tone of their voice
(33) It is difficult for me to understand why people feel the way they do*

Note: The authors permit free use of the scale for research and clinical purposes.
*These items are reverse scored.

Patient: _____ **Date:** _____

MISSOULA-VITAS® QUALITY OF LIFE INDEX

VERSION – 15R

INSTRUCTIONS:

Indicate the extent to which you agree or disagree with the following statements by marking in one of the circles below the question. If you make a mistake or change your mind, place an X through the wrong answer and mark the circle indicating your correct answer.

Today's Date: _____

GLOBAL

How would you rate your overall quality of life?

○	○	○	○	○
Worst Possible	Poor	Fair	Good	Best Possible

SYMPTOM

1. I feel sick all the time.

○	○	○	○	○
Agree Strongly	Agree	Neutral	Disagree	Disagree Strongly

2. I am satisfied with the current control of my symptoms.

○	○	○	○	○
Agree Strongly	Agree	Neutral	Disagree	Disagree Strongly

Aggregate quality of life data, without any patient identifiers, may be used for research purposes.

3. Physical discomfort overshadows any opportunity for enjoyment.

○ Agree Strongly	○ Agree	○ Neutral	○ Disagree	○ Disagree Strongly

FUNCTION

4. I am no longer able to do many of the things I like to do.

○ Agree Strongly	○ Agree	○ Neutral	○ Disagree	○ Disagree Strongly

5. I accept the fact that I can not do many of the things that I used to do.

○ Agree Strongly	○ Agree	○ Neutral	○ Disagree	○ Disagree Strongly

6. My contentment with life depends upon being active and being independent in my personal care.

○ Agree Strongly	○ Agree	○ Neutral	○ Disagree	○ Disagree Strongly

INTERPERSONAL

7. I have recently been able to say important things to the people close to me.

Agree Strongly	Agree	Neutral	Disagree	Disagree Strongly
O	O	O	O	O

8. At present, I spend as much time as I want to with family and friends.

Agree Strongly	Agree	Neutral	Disagree	Disagree Strongly
O	O	O	O	O

9. It is important to me to have close personal relationships.

Agree Strongly	Agree	Neutral	Disagree	Disagree Strongly
O	O	O	O	O

WELL-BEING

10. My affairs are not in order; I am worried that many things are unresolved.

Agree Strongly	Agree	Neutral	Disagree	Disagree Strongly
O	O	O	O	O

11. I am more satisfied with myself as a person now than I was before my illness.

Agree Strongly	Agree	Neutral	Disagree	Disagree Strongly
O	O	O	O	O

12. It is important to me to be at peace with myself.

○ Agree Strongly	○ Agree	○ Neutral	○ Disagree	○ Disagree Strongly

TRANSCENDENT

13. I have a better sense of meaning in my life now than I have had in the past.

○ Agree Strongly	○ Agree	○ Neutral	○ Disagree	○ Disagree Strongly

14. Life has lost all value for me; every day is a burden.

○ Agree Strongly	○ Agree	○ Neutral	○ Disagree	○ Disagree Strongly

15. It is important to me to feel that my life has meaning.

○ Agree Strongly	○ Agree	○ Neutral	○ Disagree	○ Disagree Strongly

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	

THANK YOU FOR YOUR COOPERATION

Name_____ Date_____

Sleep Quality Assessment (PSQI)

What is PSQI, and what is it measuring?

The Pittsburgh Sleep Quality Index (PSQI) is an effective instrument used to measure the quality and patterns of sleep in adults. It differentiates "poor" from "good" sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month.

INSTRUCTIONS:

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

During the past month,

1. When have you usually gone to bed? _____
2. How long (in minutes) has it taken you to fall asleep each night? _____
3. What time have you usually gotten up in the morning? _____
4. A. How many hours of actual sleep did you get at night? _____
   B. How many hours were you in bed? _____

5. During the past month, how often have you had trouble sleeping because you	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times a week (3)
A. Cannot get to sleep within 30 minutes				
B. Wake up in the middle of the night or early morning				
C. Have to get up to use the bathroom				
D. Cannot breathe comfortably				
E. Cough or snore loudly				
F. Feel too cold				
G. Feel too hot				
H. Have bad dreams				
I. Have pain				
J. Other reason (s), please describe, including how often you have had trouble sleeping because of this reason (s):				
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
9. During the past month, how would you rate your sleep quality overall?	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)

Scoring

Component 1	#9 Score	C1 _____
Component 2	#2 Score (<15min (0), 16-30min (1), 31-60 min (2), >60min (3)) + #5a Score (if sum is equal 0=0; 1-2=1; 3-4=2; 5-6=3)	C2 _____
Component 3	#4 Score (>7(0), 6-7 (1), 5-6 (2), <5 (3)	C3 _____
Component 4	(total # of hours asleep) / (total # of hours in bed) x 100 >85%=0, 75%-84%=!, 65%-74%=2, <65%=3	C4 _____
Component 5	# sum of scores 5b to 5j (0=0; 1-9=1; 10-18=2; 19-27=3)	C5 _____
Component 6	#6 Score	C6 _____
Component 7	#7 Score + #8 score (0=0; 1-2=1; 3-4=2; 5-6=3)	C7 _____

Add the seven component scores together _____ ***Global PSQI*** _____

A total score of "5" or greater is indicative of poor sleep quality.
If you scored "5" or more it is suggested that you discuss your sleep habits with a healthcare provider

SHORT-FORM McGILL PAIN QUESTIONNAIRE

RONALD MELZACK

PATIENT'S NAME: _____ DATE: _____

	NONE	MILD	MODERATE	SEVERE
THROBBING	0) _____	1) _____	2) _____	3) _____
SHOOTING	0) _____	1) _____	2) _____	3) _____
STABBING	0) _____	1) _____	2) _____	3) _____
SHARP	0) _____	1) _____	2) _____	3) _____
CRAMPING	0) _____	1) _____	2) _____	3) _____
GNAWING	0) _____	1) _____	2) _____	3) _____
HOT-BURNING	0) _____	1) _____	2) _____	3) _____
ACHING	0) _____	1) _____	2) _____	3) _____
HEAVY	0) _____	1) _____	2) _____	3) _____
TENDER	0) _____	1) _____	2) _____	3) _____
SPLITTING	0) _____	1) _____	2) _____	3) _____
TIRING-EXHAUSTING	0) _____	1) _____	2) _____	3) _____
SICKENING	0) _____	1) _____	2) _____	3) _____
FEARFUL	0) _____	1) _____	2) _____	3) _____
PUNISHING-CRUEL	0) _____	1) _____	2) _____	3) _____

NO PAIN |——————————————————————| WORST POSSIBLE PAIN

P P I

0	NO PAIN	_____
1	MILD	_____
2	DISCOMFORTING	_____
3	DISTRESSING	_____
4	HORRIBLE	_____
5	EXCRUCIATING	_____

Fig. 1. The short-form McGill Pain Questionnaire (SF-MPQ). Descriptors 1–11 represent the sensory dimension of pain experience and 12–15 represent the affective dimension. Each descriptor is ranked on an intensity scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe. The Present Pain Intensity (PPI) of the standard long-form McGill Pain Questionnaire (LF-MPQ) and the visual analogue (VAS) are also included to provide overall intensity scores.

Appendix 5: Neurological Examination

ΝΕΥΡΟΛΟΓΙΚΗ ΕΞΕΤΑΣΗ

Εγκεφαλικές συζυγίες:

Μυϊκή ισχύς:

- ανύψωση ώμων:
- απαγωγή άνω άκρων:
- κάμψη αντιβραχίου:
- έκταση αντιβραχίου:
- έκταση καρπού:
- έκταση δακτύλων:
- κάμψη καρπού:
- κάμψη δακτύλων:
- απαγωγή δακτύλων:
- αντίθεση αντίχειρα:
- αντίθεση μικρού δακτύλου:
- κάμψη μηρού:
- προσαγωγή- απαγωγή μηρού:
- κάμψη κνήμης:
- έκταση κνήμης:
- ραχιαία κάμψη άκρου ποδός:
- ραχιαία κάμψη δακτύλων:
- πελματιαία κάμψη άκρου ποδός:
- πελματιαία κάμψη δακτύλων:

Τενόντια αντανακλαστικά:

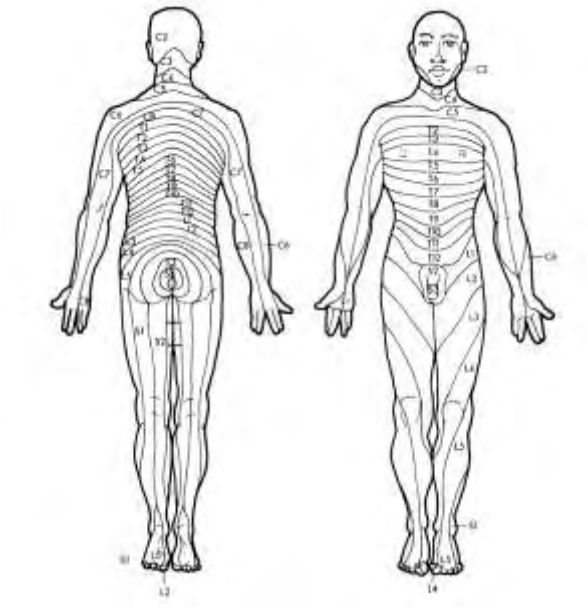
- Βραχιονοκερκιδικό:
- Δικεφαλικό:
- Τρικεφαλικό:
- Επιγονάτιο:
- Αχίλλειο:

Πέλματα:

Επιπολής αισθητικότητα:

Αφή-πίεση

Θερμό-ψυχρό



Εν τω βάθει αισθητικότητα:

Θέση μελών στο χώρο

παλλαισθησία

Παρεγκεφαλιδικές δοκιμασίες:

Βάδιση ελεύθερη, επιτηδευμένη:

ΕΥΡΗΜΑΤΑ ΝΕΥΡΟΦΥΣΙΟΛΟΓΙΚΟΥ ΕΛΕΓΧΟΥ

ΑΡΙΣΤΕΡΟ ΑΝΩ ΑΚΡΟ

NERVE	Latency (msec)	Amplitude (Mv)	NCV (m/sec)	F-wave
Median CMAP				
Ulnar CMAP				
Median SNAP				
Ulnar SNAP				

ΔΕΞΙΟ ΑΝΩ ΑΚΡΟ

NERVE	Latency (msec)	Amplitude (Mv)	NCV (m/sec)	F-wave
Median CMAP				
Ulnar CMAP				
Median SNAP				
Ulnar SNAP				

ΑΡΙΣΤΕΡΟ ΚΑΤΩ ΑΚΡΟ

NERVE	Latency (msec)	Amplitude (Mv)	NCV (m/sec)	F-wave
Peroneal CMAP				
Tibial CMAP				
Sup.Peroneal SNAP				
Sural SNAP				

ΔΕΞΙΟ ΚΑΤΩ ΑΚΡΟ

NERVE	Latency (msec)	Amplitude (Mv)	NCV (m/sec)	F-wave
Peroneal CMAP				
Tibial CMAP				
Sup peron SNAP				
Sural SNAP				

ΚΛΙΜΑΚΑ ΒΑΘΜΟΛΟΓΗΣΗΣ Της ΜΥΙΚΗΣ ΙΣΧΥΟΣ ΚΑΤΑ MRC

5/5 φυσιολογική μυϊκή ισχυς

4/5 ελαφρά πάρεση (ελάττωση μυϊκής ισχύος κατά 25% περίπου)

Πλήρης ενεργητική κίνηση

Ο μυς είναι ικανός να προσφέρει αντίσταση, αλλά όχι πλήρη

Πλήρης αντιβαρική κίνηση

3/5 μέτρια πάρεση (ελάττωση μυϊκής ισχύος περίπου 50%)

Πλήρης ενεργητική κίνηση

Ο μυς είναι ανίκανος να προσφέρει αντίσταση

Πλήρης αντιβαρική κίνηση

2/5 βαριά πάρεση (ελάττωση μυϊκής ισχύος περίπου 75%)

Περιορισμένη ενεργητική κίνηση

Ο μυς ανίκανος να προσφέρει αντίσταση

Αντιβαρική κίνηση περιορισμένη

1/5 βαρύτατη πάρεση (ελάττωση μυϊκής ισχύος περίπου κατά 90%)

Απουσία ενεργητικής κίνησης με ίχνη μόνο σύσπασης

Απουσία αντιβαρικής κίνησης

0/5 παράλυση (απώλεια ισχύος 100%)

ΕΚΤΙΜΗΣΗ ΑΝΤΑΝΑΚΛΑΣΤΙΚΩΝ

ΚΦ φυσιολογικά αντανακλαστικά

+1 ελαφριά αύξηση (χωρίς κλόνο)

+2 μέτρια αύξηση (με εξαντλούμενο κλόνο)

+3 μεγάλη αύξηση (με κλόνο μη εξαντλούμενο)

-1 ελαφριά ελάττωση

-2 μέτρια ελάττωση (μόλις παράγονται)

-3 κατάργηση των αντανακλαστικών

Appendix 6: Copyright Statement

Υπεύθυνη Δήλωση

Η κάτωθι υπογεγραμμένη NAME διδακτορική/ος φοιτήτρια/ης του Διδακτορικού Κύκλου σπουδών «ΑΣΚΗΣΗ ΚΑΙ ΥΓΕΙΑ» του Τμήματος Επιστήμης Φυσικής Αγωγής και Αθλητισμού του Πανεπιστημίου Θεσσαλίας

δηλώνω υπεύθυνα ότι αποδέχομαι τους παρακάτω όρους που αφορούν

(α) στα πνευματικά δικαιώματα της διδακτορικής Διπλωματικής Εργασίας (ΔΔΕ) μου με τίτλο «Παράμετροι κόπωσης στα χρόνια νοσήματα . Η επίδραση της άσκησης στους αιμοκαθαιρόμενους ασθενείς»

(β) στη διαχείριση των ερευνητικών δεδομένων που θα συλλέξω στην πορεία εκπόνησής της:

1. Τα πνευματικά δικαιώματα του τόμου της μεταπτυχιακής διατριβής που θα προκύψει θα ανήκουν σε μένα. Θα ακολουθήσω τις οδηγίες συγγραφής, εκτύπωσης και κατάθεσης αντιτύπων της διατριβής στα ανάλογα αποθετήρια (σε έντυπη ή/και σε ηλεκτρονική μορφή).

2. Η διαχείριση των δεδομένων της διατριβής ανήκει από κοινού σε εμένα και στον/στην πρώτο επιβλέποντα -ουσα καθηγητή -τριας.

3. Οποιαδήποτε επιστημονική δημοσίευση ή ανακοίνωση (αναρτημένη ή προφορική), ή αναφορά που προέρχεται από το υλικό/δεδομένα της εργασίας αυτής θα γίνεται με συγγραφείς εμένα τον ίδιο, τον/την κύριο-α επιβλέποντα -ουσα ή και άλλους ερευνητές (όπως πχ μέλους –ών της τριμελούς συμβουλευτικής επιτροπής), ανάλογα με τη συμβολή τους στην έρευνα ή στη συγγραφή των ερευνητικών εργασιών.

4. Η σειρά των ονομάτων στις επιστημονικές δημοσιεύσεις ή επιστημονικές ανακοινώσεις θα αποφασίζεται από κοινού από εμένα και τον/την κύριο -α επιβλέποντα -ουσα της εργασίας, πριν αρχίσει η εκπόνησή της. Η απόφαση αυτή θα πιστοποιηθεί εγγράφως μεταξύ εμού και του/της κ. επιβλέποντα -ουσας.

Τέλος, δηλώνω ότι γνωρίζω τους κανόνες περί λογοκλοπής και πνευματικής ιδιοκτησίας και ότι θα τους τηρώ απαρέγκλιτα καθ' όλη τη διάρκεια της φοίτησης και κάλυψης των εκπαιδευτικών υποχρεώσεων που προκύπτουν από το ΠΜΣ/τμήμα, αλλά και των διαδικασιών δημοσίευσης που θα προκύψουν μετά την ολοκλήρωση των σπουδών μου.

Ημερομηνία

08/01/2016

Η δηλούσα/ων

Στεφανία Γρηγορίου