UNIVERSITY OF THESSALY

Department of Physical Education and Sport Science

PhD Program

EXERCISE & HEALTH

"The effect of exercise rehabiliation regimes in combination with changes in dialysis procedures in aspects related to quality of life and health in end stage renal disease patients"

by

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Αργυρώ

Η Ιθάκη σ' έδωσε τ' ωραίο ταξίδι.
Χωρίς αυτήν δεν θάβγαινες στον δρόμο.

Κωνσταντίνος Καβάφης (1863-1933)
Ποίημα «Ιθάκη»

Abstract

Background: Hemodialysis (HD) patients suffer from various symptoms including intradialytic hypotension, heat stress, insulin resistance, muscle atrophy and fatigue, which all these parameters leading to the lack of energy and reduce patients quality of life. Lowering the dialysate temperature from 37°C (Typical dialysis; TD) to 35°C (Cold dialysis; CD) could act as an important factor in patients' hemodynamic stability during hemodialysis. It has recently been proposed that CD can improve many physiological factors including stabilizing body temperature, increasing the activity of sympathetic nervous system and consequently increasing the contraction power of the heart and the resistance of peripheral vessels. However many other benefits have been observed on patient's overall health and quality of life levels during the CD. Intradialytic exercise training (IET) it is well documented that improved functional capacity in HD patients. Moreover, intradialytic exercise can improve solute removal, dialysis adequacy, intradialytic protein synthesis, muscular strength, peak oxygen consumption, nutritional status, and quality of life. However, despite a strong rationale for the implementation of IET programs and the aforementioned benefits of CD, the separate and combined effects of exercise rehabiliation regimes in combination with changes in dialysis procedures in aspects related to quality of life and health in HD patients have not been investigated to date. The aim of the current PhD thesis was to assess the acute and chronic effect of CD and IET in parameters aspects related to glucose disposal, quality of life and health in HD patients.

Methodology: The present PhD thesis divided into 4 studies:

Study 1: Investigate the thermoregulatory responses of hemodialysis patients under four different single bouts of hemodialysis (240 min) protocols (TD, CD, TD+EX, CD+EX) (acute phase). Participates 10 HD patients age: 57.2±14.9

Study 2: To assess the separate and combined effects of CD and IET in parameters related to insulin sensitivity, health and fitness under four different single bouts of hemodialysis (240 min) protocols (TD, CD, TD+EX, CD+EX) (acute phase). Participates 10 HD patients age: 57.2±14.9

Study 3: To assess the chronic effect of intradialytic exercise training and cold dialysis in parameters related to insulin resistance and exercise capacity of patients with ESRD after 7 months of intervention (chronic phase). Participates 14 HD patients were randomized into two groups (TD+EX; mean age 63.57±9.93 & CD+EX; mean age 52.71±16.84)

Study 4: To assess the chronic effect of cold dialysis and 7-month of intradialytic exercise training (IET) on changes in vastus lateralis (VL) muscle architecture, functional capacity and quality of life in hemodialysis (HD) patients. In the first part of the study (data set 1) 14 HD

patients randomized into a CD+EX group (N = 7) and a TD+EX group (N=7). In the second part of the study (data set 2) 44 HD patients were randomized into an Exercise Group (EG=21) and a Control Group (CG=23) using the current practice (no exercise).

Results: The results of the current PhD thesis summarized below:

Study 1: The TD and TD+E protocols were associated with increased body heat storage leading to moderate effect size increases in core body temperature (as high as 0.4°C). The low temperature of the dialysate during the CD and the CD+E protocols prevented the rise in body heat storage and core temperature ($p>0.05$), even during the period that IET took place.

Study 2: None of the four different sessions have shown any statistical significant differences in glucose disposal ($p>0.05$). However, slightly numerical changes and moderate to high effect size (d:0.50-0.85) observed between TD vs CD and TD vs TD+EX in the rate of glucose and insulin disposal during the oral glucose tolerance test (OGTT). In addition, the systolic blood pressure observed statistically significant increased at the end of CD compared to TD. No statistical significant improvement observed in any aspect of functional capacity and fatigue parameters after an acute single session of CD and IET

Study 3: Insulin sensitivity index was improved by 32% in CD+EX group compared to TD+EX group. In addition, rate of glucose and insulin disposal during OGTT was improved in CD+EX group compered to TD+EX group. Functional capacity and indices of quality of life improved in both groups ($P<0.05$) independent of dialysate temperature.

Study 4: Cooling the dialysis temperature (CD) showed significant changes in VL fascicle length compared with TD (data set 1). In the second subset of data (data set 2) VL fascicle angle and length did not change significantly between the two groups ($P>0.05$) however, muscle thickness decreased in CG ($p=0.02$, $p<0.05$) while it remained unchanged in the EG. Physical performance and quality of life increased only in the EG (data set 2).

Conclusion: Reduction of dialysate temperature by 2°C induced favorable changes in aspects related to insulin sensitivity, glucose disposal, muscle architecture and the level of heat storage. Cold dialysis, also improved hemodynamic changes, occurring during dialysis reducing thus possible hypotension symptoms. Exercise training improved overall exercise capacity and indices of quality of life, irrespective dialysate temperature. Cold dialysis and Intradialytic exercise training enhances health benefits improving overall patients' quality of life. We recommended that CD with or without IET can prevent the excessive rise of body heat storage and also may provide an "acute" time-effective stimulus for improvements in glucose disposal. In addition IET provides a time-effective stimulus for increasing the functional capacity in HD

patients while larger thigh muscle architectural changes may require higher exercise training loading or supplemented with resistance exercise to reveal more clinically meaningful changes.

Περίληψη

Εισαγωγή: Οι ασθενείς με χρόνια νεφρική νόσο (ΧΝΝ) τελικού σταδίου οι οποίοι υποβάλλονται σε χρόνια αιμοκάθαρση παρουσιάζουν αρκετές διαταραχές όπως ενδοσυνεδριακή υπόταση, έντονο θερμικό στρες κατά την διάρκεια της αιμοκάθαρση, διαταραχές στο μεταβολισμό της γλυκόζης, έντονο μυϊκό καταβολισμό και μυϊκή ατροφία καθώς και γενικευμένη κόπωση, με αποτέλεσμα οι ασθενείς να υποφέρουν από έλλειψη ενέργειας οδηγώντας τους σε μειωμένη ποιότητα ζωής. Η μείωση της θερμοκρασίας του διαλύματος της αιμοκάθαρσης από τους 37°C (Τυπικής Αιμοκάθαρση, TD) στους 35°C (Κρύα Αιμοκάθαρση, CD) έχει αποδειχθεί ότι συμβάλλει σημαντικά στην αιμοδυναμική σταθερότητα των ασθενών. Μελέτες έχουν δείξει ότι η «Κρύα Αιμοκάθαρση» βελτιώνει αρκετούς φυσιολογικούς παράγοντες, όπως η αύξησης της δραστηριότητας του συμπαθητικού νευρικού συστήματος, βελτίωση της συσταλτικής ικανότητα της καρδίας και της περιφερειακής αντίστασης των αγγείων, καλύτερη διαχείριση της θερμοκρασίας του σώματος τους καθώς επίσης τους παρέχει και αρκετά οφέλη που σχετίζονται με τη γενικότερη ποιότητα της ζωής τους. Παράλληλα η ενδοσυνεδριακή άσκηση (ΕΑ) είναι καλά τεκμηριωμένο ότι βελτιώνει τη λειτουργική ικανότητα των αιμοκαθαρόμενων ασθενών. Συγκεκριμένα αρκετές μελέτες έχουν αναφέρει την ευεργετική επίδραση της ΕΑ στη βελτίωση της μυϊκής δύναμης και κατανάλωσης οξυγόνου, στην βελτίωση της ποιότητα κάθαρσης καθώς επίσης συμβάλει θετικά στη θρεπτιδική κατάσταση και ποιότητα ζωής των ασθενών κ.α. Ωστόσο, παρά τα πολυάριθμα οφέλη τόσο της ενδοσυνεδριακή άσκησης όσο και την κρύας αιμοκάθαρσης καμία μελέτη μέχρι τώρα δεν έχει εξετάσει την συνδυαστική χρόνια και οξεία επίδραση αυτών των δύο παραμέτρων.

Σκοπός: Να διερευνηθεί η χρόνια και οξεία συνδυαστική επίδραση της «κρύας αιμοκάθαρσης» και της «ενδοσυνεδριακή άσκησης» σε παραμέτρους που σχετίζονται με την υγεία και ποιότητα ζωής των ασθενών με χρόνια νεφρική νόσο (ΧΝΝ) τελικού σταδίου οι οποίοι υποβάλλονται σε αιμοκάθαρση.

Μεθοδολογία: Η παρούσα διδακτορική διατριβή χωρίζεται σε 4 μελέτες

Μελέτη 1: Διερευνήθηκαν οι οξείς θερμορυθμιστικές αποκρίσεις των αιμοκαθαρόμενων ασθενών μετά τη συμμετοχή τους σε 4 διαφορετικά πρωτόκολλα αιμοκάθαρσης (Πειραματικά πρωτόκολλα: TD, CD, TD+EX, CD+EX). Στη παρούσα μελέτη συμμετείχαν 10 αιμοκαθαρόμενοι ασθενές ηλικίας 57.2 ± 14.9.

Μελέτη 2: Αξιολογήθηκε η οξεία συνδυαστική επίδραση της «κρύας αιμοκάθαρσης» και της «ενδοσυνεδριακή άσκησης» σε παραμέτρους που σχετίζονται με την ευαισθησία στην ινσουλίνη, λειτουργική ικανότητα και την ποιότητά ζωής των αιμοκαθαρόμενων ασθενών μετά

τη συμμετοχή τους σε 4 διαφορετικά πρωτόκολλα αιμοκάθαρσης (Πειραματικά Πρωτόκολλά: TD, CD, TD+EX, CD+EX) Στη παρούσα μελέτη συμμετείχαν 10 αιμοκαθαρόμενοι ασθενές ηλικίας 57.2 ± 14.9.

Μελέτη 3: Αξιολογήθηκε η χρόνια επίδραση της «κρύας αιμοκάθαρσης» και της «ενδοσυνεδριακή άσκησης» σε παραμέτρους που σχετίζονται με την ευαισθησία στην ινσουλίνη, λειτουργική ικανότητα και την ποιότητά ζωής των αιμοκαθαρόμενων ασθενών μετά από 7 μήνες παρέμβασης. Στη παρούσα μελέτη συμμετείχαν 14 αιμοκαθαρόμενοι ασθενές ηλικίας 63.57 ± 9.93 οι οποίοι με τυχαία δειγματοληψία χωρίστηκαν σε δυο ομάδες (Πειραματικές ομάδες: Τυπική αιμοκάθαρση στους 37°C + Ενδοσυνεδριακή Άσκηση vs Κρύα Αιμοκάθαρση στους 35°C+ Ενδοσυνεδριακή Άσκηση)

Μελέτη 4: Αξιολογήθηκε η επίδραση της κρύας αιμοκάθαρσης και της ενδοσυνεδριακής άσκησης στην αρχιτεκτονική δομή του έξω πλατύ μηριαίου μυός καθώς και η λειτουργική ικανότητα των αιμοκαθαρόμενων ασθενών μετά από 7 μήνες παρέμβασης. Στη παρούσα μελέτη 14 ασθενείς οι οποίοι με τυχαία δειγματοληψία χωρίστηκαν σε δυο ομάδες (Πειραματικό πρωτόκολλο Κρύα Αιμοκάθαρση +Ενδοσυνεδριακή Άσκηση N=7 vs Τυπική Αιμοκάθαρση + Ενδοσυνεδριακή Άσκηση N=7; Data set 1.) Παράλληλα με την παρούσα μελέτη αξιολογήθηκαν ακόμη 44 αιμοκαθαρόμενοι ασθενείς όπου με τυχαία δειγματοληψία χωρίστηκαν σε δύο ομάδες (Πειραματικό πρωτόκολλο: Ομάδα ενδοσυνεδριακής άσκησης vs Ομάδα ελέγχου; Data set 2).

Αποτελέσματα: Τα αποτελέσματα της παρούσας διδακτορικής διατριβής συνοψίζονται παρακάτω:

Μελέτη 1: Κατά την διάρκεια των πρωτοκόλλων TD και TD+E παρουσιάστηκε αυξημένη συσσώρευση θερμότητας στο σώμα των ασθενών η οποία οδήγησε σε μέτριου βαθμού αύξηση της θερμοκρασίας πυρήνα του σώματος τους (έως και 0.4°C). Η μειωμένη θερμοκρασία αιμοκάθαρσης (35°C) κατά τη διάρκεια των πρωτοκόλλων CD και CD+E εμπόδισαν την αυξημένη συσσώρευση θερμότητας στο σώμα των ασθενών καθώς και της θερμοκρασίας πυρήνα του σώματος τους ($p > 0.05$), ακόμη και κατά την περίοδο της ενδοσυνεδριακής άσκησης.

Μελέτη 2: Δεν παρατηρήσαμε στατιστικά σημαντικές διαφορές μεταξύ των πειραματικών συνθηκών ($p > 0.05$). Ωστόσο, παρατηρήσαμε μικρές αριθμητικές μεταβολές και ένα μέτριο προς υψηλό effect size (d: 0,50-0,85) μεταξύ της TD και της CD, όπως επίσης και μεταξύ της TD και της TD+EX στον ρυθμό αύξησης της γλυκόζης και της ινσουλίνης στο αίμα κατά τη δοκιμασία OGTT. Επιπλέον, η συστολική αρτηριακή πίεση παρουσίασε στατιστικά σημαντική αύξηση μετά το τέλος της CD σε σύγκριση με την TD. Ωστόσο καμία στατιστικά σημαντική διαφορά

δεν παρατηρήθηκε στη λειτουργική ικανότητα και στους δείκτες κόπωσης μετά από μια συνεδρία κρύας αιμοκάθαρσης και ενδοσυνεδριακής κόπωσης.

Μελέτη 3: Παρατηρήθηκε βελτίωση του δείκτη ευαισθησίας στην ινσουλίνη κατά 32% στην ομάδα CD+EX σε σύγκριση με την ομάδα TD+EX. Επιπλέον, ο ρυθμός αύξησης της γλυκόζης και της ινσουλίνης στο αίμα κατά τη διάρκεια της OGTT βελτιώθηκε στην ομάδα CD+EX συγκριτικά με την ομάδα TD+EX. Η λειτουργική ικανότητα και οι δείκτες ποιότητας ζωής βελτιώθηκαν και στις δύο ομάδες ($p<0.05$) ανεξάρτητα από τη θερμοκρασία του διαλύματος.

Μελέτη 4: Η μείωση της θερμοκρασία του διαλλείματος φαίνεται να επηρεάζει την αρχιτεκτονική δομή του έξω πλατύ μηριαίου μυός αυξάνοντας το μήκος των μυϊκών δεματίων (Data set 1). Η γωνία πρόσφυσης και το μήκος των μυϊκών δεματιών του έξω πλατύ μηριαίου μυός δεν μεταβλήθηκαν στατιστικά σημαντικά μεταξύ των δύο ομάδων στην υποομάδα 2 ($p> 0.05$) ωστόσο το πάχος των έξω πλατύ μηριαίου μυός μειώθηκε στην ομάδα CG ($p=0.02$, $p<0.05$) ενώ παρέμεινε αμετάβλητο στην ομάδα EG. Η λειτουργική ικανότητα και οι δείκτες ποιότητας ζωής αυξήθηκαν στατιστικά σημαντικά μόνο στην ομάδα EG (Data set 2).

Συμπέρασμα: Η μείωση της θερμοκρασίας του διαλύματος της αιμοκάθαρσης κατά 2°C προκάλεσε ευνοϊκές αλλαγές στις παραμέτρου που σχετίζονται με την ευαισθησία στην ινσουλίνη, τη διάθεση της γλυκόζης, την αρχιτεκτονική του μυός και το βαθμό της θερμικής επιβάρυνσης. Η κρύα αιμοκάθαρση παρέχει σημαντικές αιμοδυναμικές αλλαγές κατά τη διάρκεια της αιμοκάθαρσης, μειώνοντας έτσι τα πιθανά συμπτώματα ενδοσυνεδριακής υπότασης που παρουσιάζουν οι ασθενείς. Η ενδοσυνεδριακή άσκησης βελτιώνει τη συνολική ικανότητα των ασθενών για άσκηση καθώς επίσης και τους δείκτες ποιότητας ζωής, ανεξάρτητα από τη θερμοκρασία του διαλύματος, ωστόσο, δεν παρουσιάζει μεγάλες αλλαγές στην αρχιτεκτονική δομή του έξω πλατύ μηριαίου μυός μεταξύ των συνθηκών CD και TD. Η κρύα αιμοκάθαρση και η ενδοσυνεδριακή άσκηση αυξάνουν τα οφέλη για την υγεία βελτιώνοντας τη συνολική ποιότητα ζωής των ασθενών. Συνιστούσαμε ότι η CD με ή χωρίς ενδοσυνεδριακή άσκηση μπορεί να αποτρέψει την υπερβολική αύξηση της συσσώρευσης θερμότητας στο σώμα των ασθενών και μπορεί επίσης να προσφέρει ένα "οξύ" χρονικό ερέθισμα για τη βελτίωση της αυξημένης γλυκόζης στο αίμα τους. Επιπλέον, η ενδοσυνεδριακή άσκηση παρέχει ένα σημαντικό ερέθισμα για την αύξηση της λειτουργικής ικανότητας των αιμοκαθαρόμενων ασθενών ενώ μεγαλύτερες μεταβολές στην αρχιτεκτονική δομή του έξω πλατύ μηριαίου μυός ίσως απαιτούν υψηλότερα φορτία άσκησης ή συμπληρωματική άσκηση αντιστάσεων για να παρατηρηθούν κλινικά σημαντικές αλλαγές.

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List of abbreviations

BAT = brown adipocyte tissue

BCM = body composition monitor

CKD = chronic kidney disease

CD = cold dialysis

CVD = cardiovascular disease

CD+EX = cold dialysis + exercise

CG = control group

ESRD = end stage renal disease

ERA = European renal association

EDTA = European dialysis and transplant association

EG = exercise group

EPO = erythropoietin

FFA = free faty acid

FWT6m = fast walking test 6 meters

GFR = glomerular filtration rate

HD = hemodialysis

HDL = high density lipoprotein

IR = insulin resistance

IET = intradialytic exercise training

KDIGO = kidney disease improving global outcomes

Kt/V = dialysate clearance of urea

6MWT = six minute walking test

NMES = neuromuscular electrical stimulation

OGTT = oral glucose tolerance test

PRT = progressive resistance training

PD = peritoneal dialysis

QOL = quality of life

RRT = renal replacement therapy

SF-36 = short form -36 questionnaire

S = body heat storage

STS-5 = sit to stand 5 repetitions

STS-60 = sit to stand 60 seconds

TD = typical dialysis

Tc = core temperature

TD+EX = typical dialysis + exercise

Tsk = mean skin temperature

USRDS = United States renal data system

UCP1 = uncoupling protein

VO2peak = oxygen uptake

VLDL = very low density lipoprotein

VL = vastus lateralis

Introduction

Chronic kidney disease (CKD) is a general term for heterogeneous disorders affecting kidney structure and function[2]. The 2002 guidelines for definition and classification of this disease represented an important shift towards its recognition as a worldwide public health problem[3]. Generally, CKD associated with advanced age, diabetes, hypertension, obesity, musculoskeletal problems and cardiovascular diseases, which is the main cause of mortality in patients with end-stage renal disease (ESRD) receiving hemodialysis therapy (HD)[4].

Despite the tremendous advances in dialysis technology, hemodialysis (HD) is a significant challenge for dialysis patients and quality of their lives[5]. Research has shown for years that dialysate fluid temperature and especially the typical dialysis (TD) temperature at (37°C) are complicated by hemodynamic instability which leading to an increased risk of heat-induced hypotension causing patient discomfort and increased mortality[6,7].

Cold dialysis (CD) is defined as the reduction of dialysis fluid temperature to 35-36°C, approximately 1°C below the typical dialysate temperature which ranges between 37-38°C[8]. A number of studies have reported beneficial effects of CD on maintaining hemodynamic stability, minimizes hypotension and exerts a protective effect over major organs including the heart and brain[9]. In addition, current evidence showed the protective effect of CD in cardiac performance during the dialysis session[10]. As we know until today cardiovascular mortality is an important issue for nephrologists that care for ESRD patients[11], however many other benefits have been observed on patients' overall health and quality of life levels by used of CD[12].

The above-mentioned benefits of CD in the hemodynamic stability and the general quality of life of the patients are highlighted even further due to the ever-increasing adoption of intradialytic exercise programs[13]. It has been well-established that intradialytic exercise leads to benefits of physiological, functional, and psychological deterioration which commonly accrues as a consequence of biological aging, catabolic illness, and a sedentary lifestyle, factors that may all contribute to the progressive decline of vitality and quality of life commonly observed in ESRD patients[14].

However, despite a strong rationale for the implementation of intradialytic exercise programs and the aforementioned benefits of CD, the separate and combined effects of these protocols in aspects related to quality of life and health in ESRD patients have not been investigated to date.

Aims – Significance

The aim of the current PhD research thesis was to assess the effect of exercise rehabiliation regimes in combination with changes in dialysis fluid temperature in aspects related to quality of life and health in end stage renal disease patients receiving hemodialysis therapy.

The primary aim of the current PhD researsh thesis was to investigate the factors involved in the phenomenon of “heat stress”, “insulin resistances” and the “changes in muscle architecture” in ESRD patients. More specific:

a. To investigate the thermoregulatory responses of hemodialysis patients under four different hemodialysis (240 min) protocols (Study 1).

b. To assess the separate and combined effects of cold dialysis and intradialytic exercise training in parameters related to insulin sensitivity, health and fitness in hemodialysis patients (acute phase) (Study 2).

c. To assess the effects of 7 months intradialytic exercise training and cold dialysis in parameters related to insulin resistance and exercise capacity in hemodialysis patients (chronic phase – Study 3).

d. To assess the changes in architecture structure of vastus lateralis muscle and functional capacity in hemodialysis patients after 7 months of intradialytic exercise training (Study 4).

The current PhD thesis is registered as a “Randomized Clinical Trial” at www.clinicaltrials.gov

Clinical Trial Registry number: NCT03905551

Literature Review

Part of the literature review has been published as follows: *Cold dialysis and its impact on renal patients' health: An evidence-based mini review. Sakkas GK, **Krase AA**, Giannaki CD, Karatzaferi C. World J Nephrol. 2017 May 6;6(3):119-122. doi: 10.5527/wjn.v6.i3.119. Review.*

2.1 Chronic kidney disease

Chronic kidney disease is defined as a reduced glomerular filtration rate, increased urinary albumin excretion, or both, and is an increasing public health issue[15]. In 2002, the US National Kidney Foundation - Kidney Disease Outcomes Quality Initiative clinical practice guidelines defined chronic kidney disease as kidney damage or glomerular filtration rate lower than 60 mL/min per 1·73 m² for 3 months or longer, and proposed a classification scheme based on glomerular filtration rate[3]. Later analyses have shown that albuminuria also has an important effect on chronic kidney disease. Improving Global Outcomes (KDIGO) Work Group on Evaluation and Management of Chronic Kidney Disease included albuminuria in the revised of 2012 classification[16,17]. Also, the National Kidney Foundation, developed a clinical practice guidelines by using an approach based on the procedure outlined by the Agency for Healthcare Research and Quality which 1) define chronic kidney disease and classify its stages, regardless of underlying cause, 2) evaluate laboratory measurements for the clinical assessment of kidney disease, 3) associate the level of kidney function with complications of chronic kidney disease, and 4) stratify the risk for loss of kidney function and development of cardiovascular disease[4]. Early identification of chronic kidney disease is needed to prevent disease progression and reduce the risk of cardiovascular morbidity and mortality.

Table 1. Classification system of chronic kidney disease

Stage	Description	GFR, mL/min per 1.73 m^2	Actions
1	Kidney damage with normal or increased GRF	≥90	Diagnosis & treatment (treatment of comorbid conditions, slowing progression CVD risk reduced.
2	Kidney damage with mild decreased GRF	60-89	Estimating of progression.
3	Moderately decreased GRF	30-59	Evaluating and treating complications.
4	Severely decreased GRF	15-29	Preparation for kidney replacement therapy.
5	Kidney failure	<15 (dialysis)	Kidney replacement (if uremia present).

Note: CVD: cardiovascular disease; GFR: glomerular filtration rate.

2.2 Epidemiology of chronic kidney disease

During the 20th century, infectious diseases were the major cause of deaths and disability. However in this century, the world's disease profile is changing, and chronic diseases now account for the majority of global morbidity and mortality. The causes of chronic kidney diseases reflect this change and diabetes, together with hypertension, is now the major cause of end-stage renal failure worldwide[18,19]. Diabetes is epidemic proportions, and its prevalence will double in the next 25 years, particularly in the developing countries. This will lead to a corresponding increase in the number of patients with chronic kidney disease and the number requiring end stage renal failure management, particularly dialysis[19].

The incidence and prevalence of end-stage kidney disease differ substantially across countries and regions. According to the 2010 Global Burden of Disease study chronic kidney disease was ranked 27th in the list of causes of total number of global deaths in 1990 (age-standardized annual death rate of 15,7 per 100 000), but rose to 18th in 2010 (annual death rate 16,3 per 100 000)[20]. White et al 2008, showed that more than 80% of all patients receiving treatment for end-stage kidney disease are estimated to be in affluent countries with large elderly populations and universal access to health care[21].

The European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) Registry (including Greece) showed that the lifetime risk of renal replacement therapy decreased with age, was lower in women as compared with men of equal age and varied considerably throughout Europe. Specifically, lifetime risk of renal replacement therapy varied from 0.44% to 2.05% at age 20 years and from 0.17% to 1.59% at age 70 years across countries and was twice as high in men as in women. Also, the lifetime risk of renal replacement therapy decreased with age, ranging from an average of 0.77% to 0.44% in 20 - to- 70-year-old women, and from 1.45% to 0.96% in 20 - to- 70-year-old men and increased slightly over the past decade, more so in men than in women[22].

2.3 Causes of chronic kidney disease

The major cause of chronic kidney disease in all developed and many developing countries is diabetes and secondarily the hypertension[15]. However, glomerulonephritis and unknown causes are more common in countries of Asia and sub-Saharan Africa, these differences are related mainly to the burden of disease moving away from infections towards chronic lifestyle-related diseases, decreased birth rates, and increased life expectancy in developed countries[23]. According to the United States Renal Data System (USRDS) the last past

decades there is a progressive increase in the number of diabetics entering end-stage renal disease therapy programs. Now, 44% of all incident patients are diabetic, while glomerulonephritis, cystic kidney disease, and hypertension have remained relatively steady as causes of end-stage renal disease[19]. In Europe and according to the European Registry Data the number of diabetics entering end-stage renal disease programs is now between 15% and 33%, while the numbers entering due to glomerulonephritis are 7% to 20%[19,24]. In developing countries, common causes of chronic kidney disease also include glomerular and tubulointerstitial diseases resulting from infections and exposure to drugs and toxins[2].

2.4 Management of chronic kidney disease

Hemodialysis (HD), peritoneal dialysis (PD), and renal transplantation are the most common renal replacement therapies worldwide and became available in the 1960s[25]. Renal replacement therapy (RRT), through either dialysis or renal transplantation, is a lifesaving yet high-cost treatment for people with end-stage kidney disease. It has been available in high-income countries for more than 50 years, with rapid growth in the number of people treated during this period[26]. Studies showed that, the number of patients which receiving RRT is projected to grow from 2.618 million in 2010 to 5.439 million by 2030. Between 2.284 and 7.083 million people who could have been kept alive with RRT in 2010 died prematurely because they did not have access to the treatment[27]. The predicted growth in the prevalence of end-stage kidney disease demands development of affordable RRT techniques and implementation of effective supplementary methods such as "cooling dialysate temperature and "intradialytic exercise" which will aim to improve the life expectancy and also, the quality of life of patients with end stage renal disease.

2.5 Common complications in ESRD patients and the effects of "cooling" dialysate temperature

2.5.1 Body Temperature and Thermal Balance during Hemodialysis

Hemodialysis is contribute on adjusting fluid and electrolyte balance and eliminating toxin waste products. The extracorporeal system of dialysis not only substitutes for part of the lost renal function but it also takes over the temperature control of the body surface because blood to be cleared in the artificial kidney is exposed to an environment with a range of different

temperatures and thermal conductivities[28]. This mechanism leading to a significant thermal perturbation in patients with end-stage renal disease (ESRD).

It well accepted that body temperature and dialysate temperature are important factors for hemodynamic stability during hemodialysis[29,30]. Van der Sande et al. (1999) showed that hemodialysis does not lead to a direct heat transfer from the extracorporeal circulation to the patient in most cases, but body temperature of the patient tends to increase during a treatment using the conventional dialysate temperature of 37°C[31].

Despite the tremendous advances in dialysis technology from the first clinical dialysis in 1924 until now, very little attention has been given to selection of dialysate temperature in ESRD patients[5]. The body temperature in humans maintained within a narrow range despite a significant rate of heat production. Heat is produced in proportion to the rate of oxygen consumption and carbon dioxide production as a results of cellular energy. Skin blood flow adjusted to regulate the heat transfer from the interior of the body to its surface. Heat production can be modified voluntarily by activity or involuntary through shivering[32,33]. However, hemodialysis is a significant challenge for thermoregulation[34]. Blood temperature can be controlled by adjusting dialysate temperature, which is important even a small changes in patient's body temperature will inevitably results in the activation of the temperature defense mechanisms[35]. Heat gained by exposure to a warm dialysate temperature must be lost by increasing skin blood flow, resulting in the delivery of warm blood to the surface of the body to maintain temperature homeostasis[5]. However, if the muscle-cutaneous nerve is blocked, cutaneous hyperaemia is prevented, which shows that this circulatory adaptation is mediated by the nervous system[36]. It is important to stress that such changes in cardiocirculatory function occur even for modest thermal variations, within the range of those that can be encountered in dialytic treatment[33].

Usually, 37°C is chosen as the typical dialysate temperature for ESRD patients underwent hemodialysis[5]. The historical reason for this is not clear, because we were unable to find any literature supporting data. However, Wunderlicch et al. (1871) in the late nineteenth century determined the concept of 37°C as normal body temperature in adults, which apparently originated from extensive studies[37].

The majority of ESRD patients have baseline body temperature below 37°C[38]. Studies showed that dialysis patients may have a lower overall temperature than healthy individuals. Why this occurs is not clear, but the fact that the body temperature of dialysis patients is

typically lower than 37°C and that a significant circadian variation exists means that using 37 as a typical reference temperature for dialysate temperature is inappropriate[39].

During hemodialysis, the hemodynamic compensation owing to ultrafiltration and hypovolemia often leads to peripheral vasoconstriction and reduced the heat loss and increased the metabolic rate[40]. This combination of decreased heat loss and increased heat production results in increased body temperature. When the dialysate temperature is equal to the body temperature the amount of heat lost through the dialyzer is less than the heat produced by the patient, resulting in an increase in body temperature[41]. The risk associated with increased in body temperature need to be considered. However, if the dialysis temperature increased in 37°C even hemodynamically stable patients may became unstable because of the heat load given by warm dialysate[42]. During hemodialysis the upright posture, intravascular volume depletion and the extracorporeal blood circulation also cause hemodynamic changes that activate baroreflexes resulting in systemic vasoconstriction (decreased skin blood flow)[5]. Concomitant with heat stress, typical dialysis in 37°C is associated, however, with hypovolaemic stress, secondarily to the removal of fluids. Hypovolaemic stress brings with it a haemodynamic response exactly opposite to the response evoked by heat: vasoconstriction instead of vasodilatation[33].

Also typical dialysis (37°C) induces acute global and segmental myocardial ischaemia[43]. Recently reported that repetitive hemodialysis induced myocardial stunning over 1 year is associated with impaired haemodynamic response to dialysis, and observations of an absolute reduction in resting ejection fraction of 10%, and development of hibernated segments of myocardium, have generated the proposal that recurrent dialysis-induced ischaemic cardiac injury may contribute to the development of ischaemic heart failure in this population[11].

Maggiore et al. (1981) proposed cooling of dialysate fluid below 36.5°C, as a factor contributing to hemodynamic stability in patients during hemodialysis[29]. Specifically, cool dialysis (CD) observed a beneficial effects avoidance of heat accumulation and hence counterproductive thermoregulatory vasodilation, and the catecholamine surge (especially during shivering) which in turn stimulate peripheral vasoconstriction and cardiac inotropy[12,44]. Also, even with modest heat storage, profound hemodynamic changes take place, including a reduction in peripheral vascular resistances, elevated heart rate, cardiac output and increased muscle sympathetic nerve activity, resulting in increased blood flow to the skin and leaving the body defenseless to hypotension, a phenomenon that does not take place during cold stress prevent intradialytic hypotension by increasing peripheral vascular resistance, improving cardiac output, and altering the levels of vasoactive peptides[39,40,45]. The majority of the CD studies using

dialysate temperatures between 35 °C-36°C[11,46]. Another important factor that CD provides significant results is intradialytic hypotension. Symptomatic hypotension is a frequent complication during haemodialysis[47]. Studies reported that 5.5%–25% of the dialysis sessions complicated by intradialytic hypotension in the cool dialysis group (CD; 35-36°C) compared with 11.2%–50% of the sessions in the typical dialysate group (TD; 37°C)[35]. These results showed that the rate of intradialytic hypotension was reduced by 70% (95% confidence interval [95% CI], 49% to 89%) with CD compared with TD[8]. CD is a very promising approach for the prevention of intradialytic hypotencion with many studies reporting improvements in haemodynamic stability including reduction in heart rate, cardiac output and stroke volume leading to high arterial blood pressure maintaining thus a greater total peripheral resistance[8,9,45].

It's important to mentioned that, CD resulted in significantly fewer nursing trips to patient's bed and even fewer interventions for the treatment of intradialytic hypotension[9]. However, the lack of long-term interventions and properly designed randomized clinical trials justifies the modest implementation of cold dialysis in the majority of the dialysis units worldwide.

2.5.2. Carbohydrate Metabolism and Insulin Resistances

Carbohydrate intolerance and abnormalities associated with uremia has been recognized for over 90 years[48]. However, the underlying mechanisms responsible for this defect still remain unclear[49]. Several studies have suggested that the glucose intolerance of uremic patients is mainly due to a) a decrease in insulin release b) a circulating insulin antagonist c) an abnormality in peripheral tissue utilization of glucose and d) a defect in hepatic storage of glycogen[49,50]. At the cellular level, uremia is associated with changes in insulin action after insulin binding to its receptor[51]. Also, studies verified that the insulin resistance (IR) occurring in patients with ESRD accompanied by impaired muscle glucose uptake and nonoxidative glucose metabolism[52]. In recent years, a growing body of evidence suggests that IR and its associated metabolic disorders are important contributors for the cardiovascular burden of patients with ESRD[53]. Specifically, new data showed that the modification of the intestinal flora and activation of inflammation pathways have been implicated in the pathogenesis of IR in obese and diabetic patients. All these pathways ultimately lead to lipid accumulation in ectopic sites and impair insulin signalling[54]. These important discoveries have led to major advances in understanding the mechanisms of uraemia induced IR.

In the 1980s, DeFronzo et al. using the 'gold standard' euglycemic hyperinsulinemic clamp technique, found evidence of IR in chronic kidney disease (CKD) patients[55]. They suggested that the site of this resistance lies in the binding of insulin to its receptor and can be reversed by dialysis[55]. It is now well established that the decline of renal function is associated with the development of IR with impaired insulin-induced glucose utilization of peripheral target tissues[56]. Since this seminal study, there has been a renewed interest in IR in CKD, especially as IR is an independent risk factor for cardiovascular morbidity and mortality in patients with CKD[56,57]

Studies showed that IR, as evidenced by reduced sensitivity to the hypoglycemic action of exogenous insulin is common in patients with ESRD[49,58]. In these patients, hepatic glucose production is not increased and is suppressed normally in response to insulin[59]. The site of IR in ESRD patients is likely to be peripheral. Since adipose tissue accounts for the disposal of less than 2% of the glucose load, the muscle tissue must represent the primary site of IR in ESRD patients[59,60]. Despite the presence of IR in almost all patients with ESRD, only 50% demonstrate glucose intolerance and hyperglycemia[61]. This is due to the variation in insulin secretory responses during hyperglycemia among ESRD patients[61]. ESRD patients with normal insulin secretory capacity can maintain normal glycaemia at the expense of hyperinsulinemia[62]. Mak (1994) showed that nondiabetic patients with ESRD often have mild fasting hyperglygemia and abnormal glucose tolerance manifested as abnormal glycemic responses during oral and intravenous glucose tolerance test[63]. However, some patients maintain normoglycemia at expence of hyperinsulinemia. On the other hand, spontaneous hypoglycemia is a complication in both nondiabetic and diabetic ESRD patients[64].

As mentioned above the metabolic clearance rate of insulin is prolonged in ESRD, but can be normalized by hemodialysis. Accumulation of dialyzable uremic toxins with progressive loss of renal function may cause inhibition of the insulin degradation system, especially by the liver, which normally removes about 50% of the insulin secreted into the portal circulation[62]. Previous studies showed that insulin sensitivity can be reduced up to 60% in nondiapetic patients with ESRD before dialysis. Marked improvement in insulin sensitivity and glucose tolerance has been reported in nondiabetic ESRD patients after 10 weeks of hemodialysis, however values did not normalize[65,66]. Another study showed that glucose intolerance can be corrected with frequent hemodialysis, but a minimal recovery period, approximately 2 weeks is necessary and the carbohydrate abnormality will reappear within 7 days if dialysis is withheld[67].

In ESRD patients undergoing maintenance haemodialysis, glycaemic control correlates closely with morbidity and mortality. Extremely high or low glycaemic levels are associated with increased morbidity and mortality owing to vascular and diabetic complications as well as malnutrition. In patients with ESRD and especially those with diabetes, glycaemic status should be closely monitored by frequent, careful measurement of glucose levels, particularly during and after each haemodialysis session. The management of hemodialysis is particularly important to reduce morbidity and mortality in this population.

Despite the strong rationale, that CD observed beneficial effect in many physiological mechanisms in patients with ESRD, limited information's exist in the literature about effects of CD in glucose metabolism and IR. Recently evidences suggest that "cold" activates brown adipose tissue[68], the benefits of CD may be related to this effect[10]. Brown adipose tissue affects whole-body metabolism, is essential for thermogenesis in human neonates and may regulate susceptibility to weight gain and insulin sensitivity[69]. It has been suggested that brown adipose tissue is unnecessary in adults, due to their higher basal metabolic rates and greater muscle mass for shivering, recent studies suggest brown adipose tissue is important for both basal and inducible energy expenditure in the form of thermogenesis, mediated by the expression of tissue-specific uncoupling protein (UCP1) in adults. Furthermore, a recent study has identified the importance of brown adipose tissue in adult humans[70]. Thus, activation of brown adipose tissue by cold may increase survival by increasing basal and inducible energy expenditure in ESRD patients[10].

2.5.3 Muscle Atrophy in ESRD patients

Several studies, the last decades showed a significant association between muscle atrophy, muscle wasting and weakness in patients with ESRD, receiving hemodialysis[71,72]. Diesel et al. (1993) showed that HD may cause disorders affecting skeletal muscle[73]. Myopathy, muscle atrophy, or uremic neuropathy occur in these patients as a result of high serum levels of calcium, urea, acidosis and low levels of carnitine and/or secondary hyperparathyroidism[74,75]. Hemodialysis is considered to have more pronounced deleterious effects on skeletal muscle, than the other replacement therapies[76]. One difference is fluctuation in toxin levels. Specifically, people on PD, dialyze every four hours or daily, whereas HD is typically conducted three times per week, and toxin levels therefore range from very low immediately after dialysis to very high before dialysis[76]. In addition, evidence showed that the permeability of the dialyzer used for HD may also contribute to the catabolic effect on muscle mass[77]. However, research advances during

the past several decades contributed much to our understanding of how chronic kidney disease its associated with comorbidities diseases, its complications and its therapies. There are many associations already reported as being associated with muscle atrophy and muscle wasting. These include decreasing glomerular filtration rate (GFR), dialysis, age, osteoporosis, cardiovascular diseases and diabetes[78-81]. Other key drivers of muscle mass in CKD include physical activity, metabolic acidosis, impaired insulin / insulin-like growth factor-1 signaling as well as inflammation[82,83]. The above situations strongly associated with increased morbidity and mortality in these patients[84,85].

In the clinical practice, fatigue is one of the most common debilitating symptoms reported by people with ESRD receiving hemodialysis and affected by muscle atrophy. The prevalence of fatigue in this population ranges from 60% to 97%[86]. Various factors including: physiological (decreased aerobic capacity and muscle strength), psychological and behavioral (anxiety, stress, depression, sleep disorders), dialysis-related (dialysis-related fatigue, frequency of dialysis, associated changes in lifestyle leading to physical limitations) and sociodemographic (employment status, social support) have been implicated as causative mechanisms associated with this fatigue[87,88]. In addition, considerable data exist that as a group, maintenance dialysis patients have low levels of physical function and that survival and hospitalization rates are directly proportional to physical performance and fatigue experienced by ESRD patients[89]. Despite the obvious importance of physical performance capacity, there are disturbing data to suggest that dialysis patients as a group have markedly lower levels of daily physical activity than healthy control subjects, to the extent that a 30 years old hemodialysis patient is likely to have less daily physical activity than a 70 years old healthy sedentary individual[13].

In general, causes of muscle weakness can include loss of muscle mass (atrophy), a decrease in the ability to generate force per unit mass or specific strength (myopathy), a reduction in the capacity of the central nervous system to activate otherwise normal motor units (central activation failure), or a combination of these mechanisms. Summarizes data from 16 studies that used muscle biopsy as a tool to evaluate morphological characteristics of skeletal muscle in people with ESRD receiving hemodialysis, showed that type II muscle fibres has major atrophy and suggested that, there is statistically significant reductions in muscle strength in all participants with ESRD[88,90]. The general observation of type II fibre atrophy in previous studies using muscle biopsy suggests the presence of weakness linked to sedentary lifestyle in people with ESRD, since type II fibre atrophy is essentially the result of disuse[88]. According to Henneman's size principle, type II motor units are the last to be recruited in voluntary actions[91].

The poor health status of people with ESRD may thus restrict activities that require large force production, necessitating recruitment of type II motor units[91]. However, Johansen et al. (2005) suggested neural mechanisms contributing to muscle weakness[92], while Fahal et al. (1997) identified causes intrinsic to the muscle[90].

Mitochondrial and other ultrastructural abnormalities have been noted in patient with ESRD with myopathy, but this possibility has not been systematically addressed[93]. The potential mechanism associated with muscle weakness in people with ESRD receiving hemodialysis could not be established, since the studies reviewed here indicated neuropathic and myopathic changes together with morphological and electrophysiological changes related to disuse atrophy. The findings of muscle damage observed on electron microscopy by Diesel et al. (1993) and Kouidi et al. (1998) are similar to changes observed following muscle damage due to eccentric contraction in people without ESRD[73,94]. These findings may support suggestions of progression of proximal muscle weakness resulting from ongoing muscle damage associated with eccentric contractions of proximal muscles carrying out their postural stabilization role during antigravity activities such as sitting on a chair, standing, or walking[95].

Many classic studies have elucidated the microscopic and ultrastructural properties of skeletal muscle fibers, yielding great insights into their function. However, less attention has been paid to the studies of the macroscopic properties of skeletal muscle tissues dating back to the 1600s[96]. This macroscopic arrangement of muscle fibers is known as a muscle's architecture[97]. Muscle architecture is a primary determinant of muscle function, understanding this structure–function relationship is of great practical importance. This understanding not only clarifies the physiological basis of force production and movement but also provides a scientific explanation of the mechanical basis of muscle injury during normal movement, and aids in the interpretation of histological specimens obtained from muscle biopsies[97,98]. The existence of relationship between muscle architecture and performance and how exercise could alter the architecture of muscles (e.g. fascicle length, muscle thickness, pennation angle etc.) have been shown in several previous studies[99,100]. Specifically Earp et al. (2010) showed that muscle architecture associated with many aspect of physical performance (e.g. running, squat movement and jumping)[101].

The varying architectural design of human and other mammalian muscles was used to illustrate the fact that muscles can be "designed" to perform fairly specific functions. Muscle architecture can change with altered muscle use or in the face of a new mechanical environment.

A detailed understanding of the mechanical and biological factors that regulate such adaptation will undoubtedly be the source of future studies[98].

In patients with ESRD as mention above, the muscle atrophy, weakness and fatigue are common symptoms and this limits their daily living and work-related activities. In this sense, the assessment of muscle architecture should be encouraged in this population. The first study that exanimate the effect of muscle architecture in ESRD patients was from Schardong et al. (2017). The study evaluated the effects of neuromuscular electrical stimulation (NMES) on muscle strength and architecture. The results showed that, there was an increase in the strength of the lower limbs in the NMES group compared to the control group and there was also a significant reduction in pennation angles of the right and left vastus lateralis muscle in the control group compared to the NMES group[102].

However, according to the literature there are no evidences about the effect of intradialytic exercise or exercise training in separate day of hemodialysis on the muscle architecture. Further studies are needed with a longer follow-up, more patients, and variables that assess other aspects besides the clinical condition, in order to further elucidate the action mechanism of muscle architecture according to exercise programs in patients with ESRD.

2.6 Intradialytic exercise training

Planned exercise, involving aerobic and resistance training modalities, has become well-recognized as a therapeutic intervention that can ameliorate the marked physiological, functional, and psychological deterioration which commonly accrues as a consequence of biological aging, catabolic illness, and a sedentary lifestyle, factors that may all contribute to the progressive decline of vitality and quality of life commonly observed in ESRD patients[14]. The efficacy of exercise training for patients with ESRD has been investigated for the past 30 years[103]. Despite the strong rationale for prescribing exercise in this patient population, barriers to regular exercise participation are many, which may explain the persistent sedentary behavior of this cohort[104].

Painter et al. (1986) conducted the first clinical trial to prescribe exercise during routine outpatient hemodialysis treatment. Fourteen patients performed up to 30 minutes of cycling using adapted cycle ergometers during the second or third hour of hemodialysis treatment 3 times/wk for 6 months. Exercising patients significantly improved peak oxygen uptake (VO2peak) by 23% after the 6 months of intervention, an extremely beneficial adaptation given that VO2peak in this cohort has been reported to be 155% less than that observed in healthy, sedentary, age-matched individuals[105].

Fortunately, up to today, many randomized controlled trials have been completed, which allows us to make a more precise and convective assessment of the effectiveness of intradialytic exercise training. Reports have shown intradialytic exercise, typically done during the first 2h of hemodialysis treatment, is a sensible non-pharmacological ‘‘medicine’’ for hemodialysis patients[106]. The most popular example of intradialytic exercise training involves placing a cycle ergometer in front of the treatment chair, or at the foot of a bed[106]. Alternatively, other novel treatments include resistance training, Zumba, guided meditation with stretching or yoga[107-109]. However, there are various exercise programs using different exercise frequencies, intensities, and duration. The intradialytic exercise training mostly consists of two or three times a week, with moderate or vigorous intensity for 30 minutes or more, and lasting from 8 weeks to 12 months[110].

There is a significant evidence to suggest that intradialytic aerobic exercise improves peak oxygen consumption (VO2peak) in ESRD patients. Johansen et al (2007) showed that there was about 17% improvement in VO2peak through aerobic exercise lasting from 8 weeks to 6 months in patients with ESRD[111]. A review on cardiovascular changes reported increases of 12% to 24% in VO2peak with exercise prescriptions of low to moderate intensity[112]. Research by Sietsema et al. (2004) revealed a distinct survival advantage for those with VO2 peak values of greater than 17.5mL·kg^{-1}·min^{-1}[113]. It also, is suggested that longer exercise interventions (>6 months) are required for the most favorable increases in VO2 peak[114]

Other reports have shown favorable changes in heart rate variability, arterial stiffness, and blood pressure[115,116]. Mustata et al. (2004) show that, 3 months of aerobic exercise training significantly improved arterial stiffness in 11 patients who are on chronic hemodialysis. The effect is transient (arterial stiffness values reverted to baseline levels 1 months after detraining). Authors suggest that the potential consequences of a sustained improvement in arterial stiffness are a decreased left ventricular afterload and hypertrophy, an increased subendocardial perfusion resulting in a better myocardial supply/demand balance, and an improvement in the mechanical stress of the large arteries[117]. Another important study performed from Miller et al. (2002) which demonstrated that hypertensive patients could significantly reduce predialysis and postdialysis systolic blood pressure after 3 months of intradialytic cycling. The reduction in blood pressure was accompanied by a reduction in antihypertensive medications[118].

Interestingly, studies have demonstrated improvements in insulin resistances. Specifically, Goldberg et al. (1979-1980) demonstrated that nondiabetic hemodialysis patients could significantly reduce fasting plasma glucose and insulin concentrations, while significantly

increasing insulin-binding affinity and glucose disappearance rate with 8–12 months of aerobic training. The authors also reported increased in fasting plasma high-density lipoprotein (HDL) cholesterol, reduced very-low-density lipoprotein (VLDL), reduced VLDL triglyceride, and reduced total plasma triglyceride secondary to aerobic exercise training[119,120]. Additionally, Storer et al. (2005) reported that 9 weeks of leg-cycling during hemodialysis improves not only cardiopulmonary fitness and endurance but also muscle strength, power, fatigability, and physical function[121]. This improvement in muscle power while using a cardiovascular mode of exercise may be due to the significant muscle weakness already experienced by the subjects[121].

Functional adaptations include improved muscle strength, exercise capacity, habitual and fastest gait speed, and ability to perform such activities of daily living as sit-to stand movements[104]. Pupim et al. (2004) showed that intradialytic exercise resulted in a nearly 4-fold increase in post-dialysis growth hormone levels. These adaptations suggest that exercise may ameliorate muscle catabolism by promoting an anabolic milieu, thereby potentially improving the clinical sequelae of sarcopenia, such as muscle weakness, falls, fractures, frailty, insulin resistance, and immune dysfunction, in hemodialysis patients[122]. Many studies reported improved muscular strength with regimens involving lower-intensity strength training[123,124]. By contrast, Moug et al. (2004) reported no significant improvement of lower body strength after 6 weeks of intradialytic cycling. This finding is not unexpected given that aerobic training is not the preferred modality for improving muscular strength, unlike resistance training[125].

Kouidi et al. (1998) reported that cross-sectional area of type I and II muscle fibers obtained from the vastus lateralis significantly increased after 6 months of combined aerobic and strength training. Ultrastructural analysis revealed that the muscle appeared more normal, including positive adaptations of the capillaries and mitochondria. The authors also noted activation of satellite cells and an increased number of leukocytes and natural killer cells[126]. However, Moore et al. (1993) observed no hypertrophy secondary to 6 months of intradialytic aerobic training, which is not unexpected given that aerobic training, is not the preferred exercise modality for eliciting myogenic adaptation[127].

Various resistance exercise programs are available for ESRD patients during hemodialysis: upper extremity strengthening with progressive resistance training (PRT) with free-weight dumbbells, lower extremity strengthening with weighted ankle cuffs, or use of the Thera-band stretch strap in a sitting position are used[110]. Johansen et al (2006) have shown an increase in quadriceps muscle cross-sectional area and an improvement in self-reported physical functioning by lower extremity resistance exercise training for 12 weeks during hemodialysis

sessions three times per week with the use of ankle weights[128]. In addition, Cheema et al (2007) suggested that patients with ESRD could improve skeletal muscle quality and derive other health-related adaptations solely by engaging in a 12-week high-intensity, progressive resistance training regimen during routine hemodialysis treatment sessions[87].

Furthermore, research findings show improvements in fatigue levels, depression, quality of life, sleep, restless legs, inflammation, dialysis adequate and hospitalization rates.[129-131] Zaluska et al. (2002) has demonstrated an improvement in dialysis adequacy (Kt/V) with 6 months of intradialytic aerobic training using cycle ergometers[132]. Evidence suggests that a single, acute bout of intradialytic cycling can significantly enhance the removal of urea, creatinine and potassium during hemodialysis by significantly reducing post-dialysis rebound of these damaging solutes. Intradialytic exercise training could enhance dialysis adequacy chronically via this same mechanism[104,133].

In conclusion, it is important to note that after years of research on the benefits and safety of intradialytic exercise, a movement needs to occur toward application. Success with such a program requires a deliberate choice by policy makers and management to bring about a whole-team approach to exercise. While many excellent programs are nurse-led, an exercise professional may be instrumental in creating a ‘‘culture of exercise’’ within the dialysis unit, and this person should not be considered a ‘‘luxury’’ but rather a necessity and essential player in enhancing health care[103]. Furthermore, encouraging better self -management for high-risk patients may result in a reduced burden to overwhelmed health care systems[93].

2.7 Quality of life in patients with ESRD

Several sociodemographic and clinical variables are known to influence the health-related quality of life (QOL) of patients with ESRD. Currently, the management of patients with ESRD undergoing hemodialysis includes among its objectives the assessment of health-related quality of life aimed at its improvement or preservation[134]. Studies showed that after dialysis is initiated, patients with ESRD experience considerable inconveniences. During hemodialysis, patients have to spare four hours a day, three days a week regardless of individual schedules. In addition, it is hard for dialysis patients to maintain their job, which ultimately lowers their socioeconomic status. Therefore, it is natural for chronic kidney disease patients to be unhappy, and the overall health-related quality of life cannot be high with the progression of chronic kidney disease[135].

Several studies the last decades tried to assessed the effect of cooling dialysate temperature and intradialytic exercise in evaluation of Medical Outcomes Trust Short-Form 36

(SF36) which scores as health-related QOL outcome measures[136]. Specifically, many studies showed that intradialytic exercise can improved the perceptions of 'physical functioning' secondary after to 3–5 months of aerobic and combined training[137,138]. Oh-Park et al. (2002) showed that combined training performed during hemodialysis can improved also 'mental health' scores[139]. However, remarkable was the fact that Painter et al (2001) reported improvements in other SF-36 QOL domains including: 'role physical', 'bodily pain', 'general health, 'vitality' and the 'physical component scale' after exercise, especially in patients with low baseline perceptions of physical functioning[140]. In contrast, DePaul et al (2002) showed that aerobic and muscle strength training did not yield improvements in any SF-36 scores. However, the authors speculated that the lack of significance could be due to the fact that their patients had high functional status at baseline and/or their study was inadequately powered[141].

In a meta-analysis that carried out by Sheng et al (2014) indicates that intradialytic exercise had significant effects on the physical function of life, but there was no significant difference in the mental function[142]. Another important factor that can improve during regular exercise in these patients, it is the anxiety and depression, which is very important factors in maintaining the quality of life of patients. Suh et al (2002) indicate that an appropriate application of exercise program would improve the psychological status in long-term maintenance hemodialysis patients[143].

Despite the positive effects of intradialytic-exercise training in patient's QOL, the effects of "cooling" dialysate temperature in patient's QOL are ambiguous. The study of Selby et al. (2006) was the only trial that reported the effect of cool dialysis on QOL. Specifically, in this trial, there was no difference between cool and standard dialysis on QOL using the short form 36 health survey assessment tool[144]. Additionally, Ayoub and Finlayson (2004), although not clearly assessing QOL, did indicate that 80% of the patients receiving cool dialysis self-reported a dramatic improvement in their general health[6]. Also, Parker et al. (2007) have found that the use of cooling dialysate temperature may improve nocturnal sleep (which is another aspect of quality of life) by decreasing sympathetic activation and sustaining the nocturnal skin temperature[145].

However, the poor reporting of symptoms and the lack of systematic evaluation of their quality of life severity in ESRD patients continue to limit the ability to accurately assess the effect of cool dialysis on patient's quality of life.

Research Study 1

Separate and combined effects of cold dialysis and intradialytic exercise on the thermoregulatory responses of patients with end-stage renal disease

Under Review**:** Separate and combined effects of cold dialysis and intradialytic exercise on the thermoregulatory responses of patients with end-stage renal disease. **Argyro A. Krase MSc**, Andreas D. Flouris PhD , Christina Karatzaferi PhD, Ioannis Stefanidis MD, PhD, Giorgos K. Sakkas PhD. Submitted in American Journal of Kidney Diseases [AJKD01117-2019]

Abstract

Background: Intradialytic exercise training (IET) and cold dialysis (CD) at 35°C dialysate temperature can be beneficial for hemodynamic stability during hemodialysis, but the separate and combined effects of these methods on patient thermoregulation remain unknown. This study assessed the thermoregulatory responses of hemodialysis patients under four different hemodialysis protocols: a) one typical dialysis (TD) protocol (dialysate temperature at 37°C), b) one CD protocol (dialysate temperature at 35°C), c) one TD protocol which included a single exercise bout (TD+E), d) one CD protocol which included a single exercise bout (CD+E). **Methods:** Ten haemodialysis patients (57.2±14.9 years) participated in the study. Core and skin temperatures were measured using an ingestible telemetric pill and by four wireless iButtons attached on the skin, respectively. Body heat storage calculated using the thermometric method proposed by Burton. **Results:** The TD and TD+E protocols were associated with increased body heat storage leading to moderate effect size increases in core body temperature (as high as 0.4°C). The low temperature of the dialysate during the CD and the CD+E protocols prevented the rise in body heat storage and core temperature ($p>0.05$), even during the period that IET took place. **Conclusion:** TD and IET are accompanied by a moderate level of hyperthermia, which can be offset by CD. We recommended that CD or with IET can prevent the excessive rise of body heat storage. **Clinical Trial Registry number:** NCT03905551.

Keywords: cold dialysis, body temperature during dialysis, dialysis temperature, thermal balance

Introduction

Hemodialysis (HD) represents a significant challenge for the thermoregulatory system of HD patients[146,147]. Indeed, body temperature rises during HD due to (i) heat transfer into the body via the heated dialysate, (ii) endogenous heat production through normal metabolic processes, and (iii) attenuated heat loss at the skin surface[47]. The latter has been hypothesized to occur because cutaneous vessels are constricted during typical dialysis (TD; 37°C dialysate temperature) due to loss of blood volume towards the extracorporeal circuit[148]. This leads to attenuated heat dissipation from the skin surface despite the fact that metabolic heat production remains relatively stable[41]. Consequently, heat is accumulated (this is typically referred to as "increased body heat storage") and, soon, core temperature rises during a typical session of hemodialysis[149]. This increased heat storage (S) offsets the vasoconstrictive response to hypovolemia[35] and it is one of the responsible contributing factor which leading to the intradialytic hypotension causing patient discomfort and increased mortality[150,151].

Lowering the dialysate temperature (35-36°C; cold dialysis) has been proposed as a simple and useful method to reduce heat storage during hemodialysis and, therefore, decrease the frequency of intradialytic hypotension episodes[41,152,153]. Indeed, cold dialysis (CD) attenuates the risk for patient hyperthermia compared to typical dialysis (dialysate temperature at 37°C; TD) and leads to cutaneous vasoconstriction[154]. These observations have led to a growing interest in the thermal and circulatory adaptations occurring during CD[155]. Yet, the precise changes in body heat balance during either CD or TD remain poorly documented and understood.

The above-mentioned benefits of CD in thermoregulatory and cardiovascular stability are highlighted even further due to the well accepted adoption of intra-dialytic exercise training programs[14]. It has been well-established that intra-dialytic exercise leads to benefits in strength and endurance[14,156,157] as well as improved clearance (Kt/v)[158], hemodynamic stability, and patient quality of life[14]. The beneficial effects of intradialytic-exercise are due to increased muscle blood flow and reduced inter-compartmental resistance by peripheral vasodilation[159]. Overcoming this resistance seems to be the single most effective method for improved toxin removal during hemodialysis[160]. Nevertheless, this vasodilation is augmented further during TD by the exercise-induced hyperthermia[159] and may, therefore, increase the frequency of intradialytic hypotension episodes. As indicated above, we hypothesized that CD may be able to minimize the need for peripheral vasodilation, leading to improved patient thermoregulatory and cardiovascular stability.

However, despite a strong rationale for the implementation of intradialytic exercise training programs and the aforementioned benefits of CD, the separate and combined effects of these protocols on patient thermoregulation have not been investigated to date.

The aim of the current study was to assess the thermoregulatory responses of hemodialysis patients under four different hemodialysis (240 min) protocols: a) one TD protocol (dialysate temperature at 37°C), b) one CD protocol (dialysate temperature at 35°C), c) one TD protocol which included a single exercise bout (TD+E), d) one CD protocol which included a single exercise bout (CD+E).

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 General Hospital of Trikala, Greece. All patients gave their written informed consent prior to study participation.

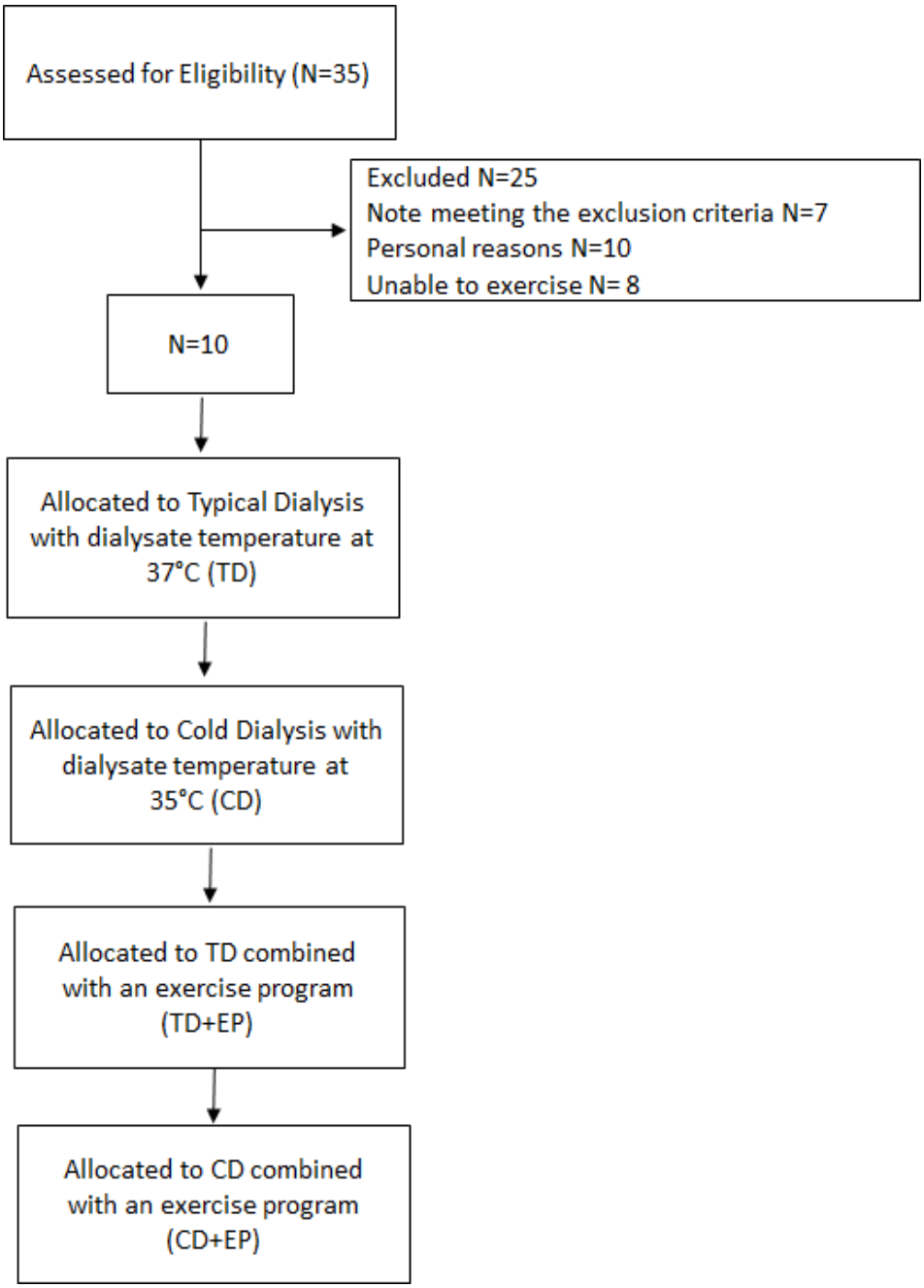
Study Design

Ten haemodialysis patients were recruited from a single haemodialysis unit at the General Hospital of Trikala, Thessaly, Greece. The study was performed from October 2016 to June 2018. All study measurements were performed at a hospital climate control room using the metabolic ward of the General Hospital of Trikala, Greece. The mean age was 57.2±14.9 years (Table 1). Patients enrolled by a research assistant assigned into the study while the order that the patients assigned to the first scenario was random using a computer random number generator. Each patient was monitored during a) one session of typical dialysis with dialysate temperature at 37°C (TD), b) one session of cold dialysis with dialysate temperature at 35°C (CD), c) one session of TD combined with an exercise program (TD+EP), d) one session of CD combined with an exercise program (CD+EP). The patient participants underwent hemodialysis therapy (Fresenius 4008B, Oberursel, Germany) three times per week with low flux, hollow fiber dialyzers and bicarbonate buffer, with the hemodialysis protocol lasting 4 hours. The dialysis protocols were performed using dialysis flow at 550ml/min and mean average of conductivity dialysance at 137-140 mEq/Λ. All patients were clinically stable and they had received regular hemodialysis treatment for at least 3 months, with adequate dialysis delivery Kt/V >1.1 and good compliance of dialysis treatment, the serum albumin was >2.5 g/dL, hemoglobin ≥11g/dL and treated with rHuEPO. Patients were not eligible for participation in the study if they had a reason to be in a catabolic state, such as hyperthyroidism, active vasculitis, malignancies, pregnant HIV, opportunistic infections, musculoskeletal contraindication to exercise, requirement for systemic anticoagulation, participant or participated in an investigational drug or medical device study within 30 days or five half-lives or inflammations, that required intravenous antibiotics within 3 months prior to enrollment, diabetics receiving insulin therapy, New York Heart Association grade IV heart failure, and mental incapacity to consent.

Dialysis protocols were performed in a random order at the same time and day of the week to minimize differences in ultrafiltration volume between the four protocols. The ambient temperature in the room was 25.2-25.9°C. Food consumption was not allowed during the dialysis

procedure. During the different dialysis protocols, core temperature (T_C) and mean skin temperature (T_{sk}) were recorded. The body heat storage (S) for every minute was calculated during all conditions using the thermometric method proposed by Burton. The data recording lasted five hours for each patient (1 hour before dialysis protocol and 4 hours during the dialysis protocol). The exercise program during TD+E and CD+E was performed between the 60th and the 120th minute of the dialysis protocol.

Figure 1: Chat flow of study design



Core temperature measurements (T_c)

Core temperature (T_c) was measured at the gastrointestinal tract using an ingestible telemetric pill. Data recorded continuously at 1-minute intervals, throughout the course of the experimental intervention. The telemetric pill was ingested by the patients 7-hour before arriving in the hospital[161,162].

Mean Skin temperature measurements (T_{sk})

Skin temperature was measured at 1-minute intervals by wireless iButtons (iButton, Maxim, USA). The iButtons were programmed before their application on the skin, as outlined by the manufacturer. The iButton resolution was set at 0.06ºC and the iButton real-time clock was synchronized with a laptop computer. The iButtons were attached on the skin using water-resistant, medical-grade tape. In total four iButtons were attached on the skin, at the following anatomic locations: on the biceps, pectoralis major, rectus femoris, and gastrocnemius, and were used to calculate mean skin temperature (T_{sk}) using Ramanathan equation[163].

Body heat storage (S)

Body heat storage for every minute was calculated during all conditions using the thermometric method proposed by Burton: $S=3.47 \cdot m_b \cdot \Delta \dot{T}b$ where 3.47 is the average specific heat of body tissues (in $kJ \cdot kg^{-1} \cdot °C^{-1}$), m_b is the patient's body mass (in kg), and $\Delta \dot{T}b$ is the rate of change in mean body temperature ($\dot{T}b$) at time t t from the beginning of HD (initial $\dot{T}b$ at time 0)[164].

Intradialytic Exercise Program

The patients performed cycling for 60 minutes in the supine position. During the TD+EP and CD+EP protocols, the patients were asked to pedal on a bedside cycle ergometer (Model 881 Monark Rehab Trainer, Monark Exercise AB, Varberg, Sweden) at 40 rpm for the first 10 minutes and then at 50 rpm. Patients cycled at approximately 60% of their pre-assessed maximum power capacity. The exercise regime started 1h after the commencement of the hemodialysis session. The patients' maximum power capacity was determined by a modified version of the Åstrand Bicycle Ergometer Test protocol at bedside on a previous dialysis session during hemodialysis. Exercise was well tolerated by all patients, and no adverse reactions were reported.

Sample size estimation

The minimum required sample size was determined using data from a previous study[165] where 17 hemodialysis patients underwent CD aiming to reduce TC from 36.4±0.4°C at baseline to 36.1±0.1°C at the end of the dialysis protocol. Sample size calculations were conducted using G*Power 3.0[166]. The "Means: difference between two dependent means" method was used to calculate the power of the within effect. A two-tailed test selected. Statistical power and α error probability were set to 0.80 and 0.05, respectively. The minimum required sample size was determined by calculating the effect size d. Using the aforementioned published data, the resulting minimum required sample size was 10 participants.

Statistical analysis

A Multivariate Analysis of Variance (MANOVA) followed by post-hoc paired-samples t tests were used to assess the effects of time (-30, 0, 30, 60, 90, 120, 150, 180, 210, 240) and protocol (TD, CD, TD+E, CD+E) on T_C, T_{sk}, and S. The MANOVA results demonstrated no statistically significant main or interaction effects. However, the observed power in these tests ranged between 0.17 and 0.67 (with the exception of the protocol main effect in T_C which was 0.96). Given the very low power of these tests, the analysis was focused exclusively in the post-hoc paired-samples t tests. To further strengthen the analysis, Cohen's d effect sizes (0.2-0.5: small effect; 0.5-0.8: moderate effect; >0.80: large effect) were also used to identify paired differences between protocols and times. Data are expressed in mean±SD. A p value <0.05 was considered statistically significant. All analyses were carried out using the Statistical Package SPSS 21.

Results

Ten stable chronic hemodialysis patients were eligible and consent to participated in the study. All participants completed all 4 scenarios during hemodialysis on a random order. The patient's characteristics are presented in Table 1.

Table 1. Individual characteristics of the study group

Patient (n)	Age (yr)	Sex	Dry Weight (kg)	Height (cm)	Body surface area (m^2)	Cause of end-stage renal disease
1	82	M	69.7	161	1.77	Glomerulonephritis
2	51	M	73.6	175	1.90	Nephrectomy
3	65	M	69.0	185	1.88	Polycystic kidney disease
4	63	M	80.0	175	1.97	Glomerulonephritis
5	61	M	80.5	178	2.00	Glomerulonephritis
6	61	F	64.2	158	1.68	Polycystic kidney disease
7	32	M	66.0	173	1.78	IgA nephropathy
8	53	M	85.3	174	2.03	Polycystic kidney disease
9	68	M	78.8	172	1.94	Unknown causes
10	36	M	48.3	145	1.39	Glomerulosclerosis

Note: mean±sd; Age: 57.2±14.9; Dry Weight: 71.4±10.0; Height: 169.6±11.6; Body Surface: 1.83±0.18

TD protocol vs CD protocol

The TD resulted in an increase of core body temperature (T_C) compared to CD (TD: 36.9±0.1°C; CD: 36.7±0.2°C; Table 2). This was evident by statistically significant differences between CD and TD from 0 to 180 min ($p<0.05$) as well as large effect sizes ($d>0.8$) observed from 0 to 150 min and a moderate effect size ($d=0.5$-0.8) observed at 180 min (Table 2). The skin temperature (T_{sk}; TD: 31.0±0.6°C; CD: 31.3±0.4°C) and S (TD: 5.5±40.5 W; CD: 19.3±37.7 W) were similar during the two protocols ($p>0.05$ and $d<0.4$; Table 2).

TD protocol vs TD+E protocol

The T_C remained similar during the TD+E and the TD protocols (TD: 36.9±0.1°C; TD+E: 36.9±0.2°C) except during the period that exercise training took place, where a slight increase in T_C was evident (TD: 36.9±0.1°C; TD+E: 37.0±0.1°C) resulting in a medium effect size observed at the end of exercise (Table 2). The T_{sk} was increased during the TD+E protocol throughout the dialysis session (31.0±0.6°C; TD+E: 31.7±0.8°C) resulting in moderate effect sizes observed at 30, 210, and 240 minutes in the protocol (Table 2). Overall, the S was slightly

increased during the TD+E protocol (TD: 5.5±40.5W; TD+E: 11.2±141.4W) and particularly during the exercise period, as indicated by moderate effect sizes (Table 2).

TD protocol vs CD+E protocol

The T_C during the CD+E protocol was lower than during the TD (TD: 36.9±0.1°C; CD+E: 36.6±0.2°C), which was evident by significant reductions ($p<0.05$) and moderate/large effect sizes until 180 min into the protocol (Table 2). These differences were also observed during the exercise period of the CD+E (TD: 36.9±0.1°C; CD+E: 36.7±0.1°C). The skin temperature (T_{sk}; TD: 31.0±0.6°C; CD+E: 31.3±0.9°C) and S (TD: 5.5±40.5 W; CD+E: 2.2±112.5 W) were similar in both protocols ($p>0.05$ and $d<0.4$; Table 2).

CD protocol vs TD+E protocol

The T_C increased almost throughout the TD+E protocol compared to the CD (CD: 36.7±0.2°C; TD+E: 36.9±0.2°C), which was evident by statistically significant differences ($p<0.05$) and moderate/large effect sizes (Table 2). In addition, the TD+E protocol resulted in somewhat increased T_{sk} (CD: 31.3±0.4°C; TD+E: 31.7±0.8°C) which was observed via moderate effect sizes at different points (i.e., 30, 120, and 210 min) during the protocol. Similarly, the S was somewhat increased during the TD+E protocol (CD: 19.3±37.7W; TD+E: 11.2±141.4W), observed via moderate effect sizes at different points (i.e., 30, 150, and 240 min) during the protocol.

CD protocol vs CD+E protocol

During the exercise period of the CD+E protocol (CD: 36.5±0.1°C; CD+E: 36.7±0.1°C), the T_C was significantly increased compared to the CD ($p<0.05$ and moderate effect sizes from 60 to 90 min), yet the low dialysate temperature used in the CD+E was able to disseminate this additional amount of heat (Table 2). As a result, the T_C was similar across the CD and the CD+E protocols (CD: 36.7±0.2°C; CD+E: 36.6±0.2°C). Similar effects were observed for T_{sk} where values were slightly increased during the exercise period of the CD+E protocol (CD: 31.3±0.4°C; CD+E: 31.7±0.9°C), paralleled with a p value of 0.08 and a moderate effect size at 120 min (Table 2). However, there was no overall T_{sk} differences between the CD and the CD+E protocols (CD: 31.3±0.4°C; CD+E: 31.3±0.9°C). The slight increases in T_C and T_{sk} during the CD+E were also evident in terms of S, where moderate/large effect sizes were observed at different time points (i.e., 30, 60, 120, 150, and 240 min; Table 2). However, as a whole, there

were no major differences in S between the two protocols (CD: 19.3±37.7W; CD+E: 2.2±112.5W).

TD+E protocol vs CD+E protocol

The T_C was increased throughout the TD+E protocol compared to the CD+E (TD+E: 36.9±0.2; CD+E: 36.6±0.2°C), evident by statistically significant differences ($p<0.05$) and moderate/large effect sizes observed in most of the tested time points (Table 2). Similarly, the TD+E protocol resulted in somewhat increased T_{sk} (TD+E: 31.7±0.8°C; CD+E: 31.3±0.9°C; Table 2). In terms of S, the CD+E led to attenuated values compared to TD+E, particularly during the exercise phase, as evidenced by moderate effect sizes (Table 2).

Table 2. Results and comparisons for core body temperature (T_C), mean skin temperature (T_{sk}) and body heat storage (S) in the four different dialysis protocols.

Time (min)	Results for each protocol (mean±sd)				Post hoc comparisons between protocols (p-value[effect size])					
	TD	CD	TD+E	CD+E	TD vs CD	TD vs TD+E	TD vs CD+E	CD vs TD+E	CD vs CD+E	TD+E vs CD+E
					T_C (°C)					
-30	36.80±0.28	36.70±0.16	36.60±0.59	36.40±0.32	0.26[0.43]	0.34[0.41]	0.00[1.27]	0.73[0.22]	0.02[1.17]	0.48[0.39]
0	36.80±0.20	36.60±0.19	36.60±0.61	36.40±0.29	0.00[0.98]	0.36[0.41]	0.00[1.54]	0.94[0.00]	0.12[0.80]	0.55[0.38]
30	36.80±0.20	36.50±0.25	36.80±0.34	36.60±0.28	0.00[1.26]	0.78[0.00]	0.04[0.79]	0.00[0.96]	0.18[0.36]	0.07[0.60]
60	36.80±0.22	36.50±0.30	36.90±0.37	36.70±0.33	0.00[1.08]	0.38[0.31]	0.30[0.34]	0.00[1.14]	0.00[0.61]	0.00[0.54]
90	36.90±0.25	36.50±0.34	37.00±0.35	36.70±0.39	0.01[1.25]	NA[0.31]	0.21[0.58]	0.00[1.39]	0.03[0.53]	0.00[0.78]
120	36.90±0.32	36.60±0.35	37.00±0.38	36.60±0.40	0.00[1.24]	0.26[0.41]	0.03[1.23]	0.00[1.66]	0.39[0.00]	0.00[1.65]
150	37.00±0.33	36.60±0.39	37.00±0.36	36.60±0.40	0.00[1.04]	0.40[0.00]	0.00[1.03]	0.00[1.02]	0.73[0.00]	0.00[1.00]
180	37.00±0.33	36.80±0.41	37.00±0.33	36.60±0.38	0.06[0.51]	0.31[0.00]	0.04[1.06]	0.00[0.51]	0.05[0.48]	0.00[1.07]
210	36.90±0.40	37.00±0.40	37.01±0.31	36.80±0.38	0.65[0.24]	0.01[0.30]	0.96[0.24]	NA[0.03]	0.06[0.49]	0.00[0.58]
240	36.90±0.57	37.01±0.40	37.01±0.30	36.90±0.38	0.18[0.22]	0.13[0.24]	0.34[0.00]	0.47[0.00]	0.15[0.27]	0.02[0.31]
					Tsk (°C)					
-30	30.80±2.39	30.70±1.71	32.30±2.36	31.80±0.79	0.74[0.05]	0.52[0.59]	0.39[0.52]	0.00[0.74]	0.18[0.76]	0.13[0.26]
0	30.10±2.68	31.70±2.00	30.90±2.39	32.00±2.21	0.45[0.65]	0.38[0.29]	0.36[0.73]	0.25[0.35]	0.19[0.14]	0.31[0.45]
30	30.60±2.95	31.70±1.58	32.60±2.13	32.40±1.48	0.95[0.45]	0.25[0.71]	0.15[0.70]	0.30[0.46]	0.65[0.42]	0.42[0.10]
60	30.80±2.67	31.70±2.51	31.30±0.71	31.40±2.22	0.74[0.32]	0.54[0.22]	0.97[0.23]	0.74[0.18]	0.48[0.12]	0.52[0.05]
90	30.80±2.92	31.30±2.13	30.30±3.11	30.90±2.02	0.25[0.19]	0.70[0.15]	0.92[0.04]	0.90[0.36]	0.52[0.18]	0.74[0.22]
120	32.20±3.38	31.00±2.43	32.70±2.12	32.70±2.22	0.59[0.40]	0.62[0.17]	0.97(0.17]	0.07[0.69]	0.08[0.69]	0.70[0.00]
150	31.60±3.04	30.90±1.70	30.80±1.76	30.90±2.48	0.51[0.29]	0.81[0.30]	0.71[0.24]	0.37[0.05]	0.29[0.00]	0.28[0.04]
180	30.60±2.97	31.00±3.14	31.70±2.78	30.60±3.09	0.76[0.12]	0.80[0.35]	0.67[0.00]	0.27[0.22]	0.69[0.12]	0.81[0.35]
210	30.70±2.68	31.10±1.41	32.40±0.92	29.60±2.68	0.84[0.19]	0.32[0.82]	0.73[0.38]	0.01[1.00]	NA[0.69]	0.06[1.30]
240	31.60±0.66	32.00±1.52	32.00±0.79	31.10±2.86	0.65[0.28]	0.44[0.49]	0.90[0.20]	0.94[0.00]	0.69[0.38]	0.87[0.40]
					S (W)					
0	-54.34±182.6	34.17±210.50	-84.20±295.36	-33.85±238.71	0.45[0.42]	0.89[0.12]	0.41[0.09]	0.90[0.45]	0.35[0.28]	0.39[0.17]
30	39.01±187.0	-6.15±159.41	159.14±215.85	74.10±192.75	0.45[0.25]	0.39[0.56]	0.39[0.17]	0.41[0.84]	0.10[0.43]	0.56[0.38]
60	50.58±219.8	-5.69±262.82	19.07±308.96	-135.94±222.3	0.96[0.21]	0.80[0.30]	0.19[0.39]	0.75[0.08]	0.82[0.48]	0.16[0.52]
90	8.35±74.70	1.59±190.49	-167.15±350.7	-30.79±263.21	NA[0.04]	0.33[0.67]	0.90[0.18]	0.54[0.58]	0.30[0.13]	0.51[0.42]
120	45.09±35.09	-13.95±208.01	258.26±323.77	82.40±221.48	0.63[0.31]	0.29[0.75]	0.94[0.19]	0.32[0.96]	0.54[0.42]	0.57[0.59]
150	-58.33±83.87	-9.64±171.71	-156.35±174.0	-158.86±146.5	0.73[0.30]	0.42[0.61]	0.17[0.72]	0.42[0.79]	0.12[0.86]	0.90[0.01]
180	27.94±173.5	44.30±281.96	16.24±143.47	38.42±219.26	0.58[0.06]	0.75[0.07]	0.68[0.05]	0.70[0.11]	0.79[0.02]	0.59[0.11]
210	-1.24±161.2	26.64±260.76	88.58±189.02	-19.50±360.73	0.45[0.11]	0.14[0.45]	0.81[0.06]	0.68[0.25]	0.76[0.14]	0.51[0.35]
240	-7.32±151.2	102.73±87.93	-32.87±95.20	203.34±181.97	0.63[0.89]	0.91[0.19]	0.21[1.10]	0.37[1.38]	0.57[0.69]	0.01[1.54]

Note: TD: typical dialysis (dialysate temperature 37°C); CD: cold dialysis (dialysate temperature 35°C); TD+E: one TD protocol which included a single exercise bout; CD+E: one CD protocol, which included a single exercise bout. Post hoc tests indicate comparisons between different protocols at the same time point; grey lines indicate results during the exercise program; time points at -30 and 0 minutes indicate the pre-dialysis period; time points from 30 to 240 indicate the dialysis period; NA indicates instances when post hoc tests were not conducted due to high number of missing values.

Discussion

The present study, sought to examine for the first time the separate and combined effects of cold dialysis and intradialytic exercise training on the thermoregulatory responses (core temperature, skin temperature, and body heat storage) of stable hemodialysis patients using for the first-time whole-body direct temperature assessment tools. Our results demonstrated that the TD and TD+E protocols are associated with increased body heat storage leading to moderate increases in core temperature (as high as 0.4°C). Such changes in body heat storage and core temperature are known to cause peripheral vasodilation[167,168] and may offset the vasoconstrictive response to hypovolemia[35] which is responsible for intradialytic hypotension causing patient discomfort and increased mortality[46,151]. Therefore, the present detailed thermoregulatory assessment results confirm previous evidence suggesting that TD represents a challenge for the thermoregulatory system of patients with end-stage renal disease especially in developing countries where dialysis units ambient conditions are inadequately controlled[146]. In contrast, the low temperature of the dialysate during the CD and the CD+E protocols prevented the rise in body heat storage and core temperature, even during the period that exercise training took place.

It has been well-established that intra-dialytic exercise leads to benefits in physical performance and quality of life in hemodialysis patients[14]. Our results demonstrated that during exercise phase and especially when the dialysis temperature was at 37°C, body heat storage slightly increased (Fig 1). Studies show that during the intradialytic exercise an increased in skin blood flow limits the cardiovascular adjustment needed for work, because skin circulation participated both in hemodynamic control and thermoregulation[14].

Even though the uniqueness of our study as well as the laborious methodology and highly skilled personnel required a number of limitations unfortunately still remain. It is important to denote that we were unable to obtain peripheral/skin blood flow data assessing the blood redistribution occurred during the 4 different scenarios. Therefore, our inferences regarding peripheral vasoconstriction/vasodilation stem from skin temperature measurements. Nevertheless, it is well known that skin temperature is very well correlated with changes in the cutaneous circulation[167,168]. Another issue to consider is the effect of fixed reduction in dialysate temperature. As a consequence, the dialysis treatment must be adapted to the patient's individual condition and response to treatment. Indeed, recent reports support the link between cold dialysis and low intradialytic hypotension episodes in the hypotensive HD patients[9].

Conclusion

In conclusion, the results of the present study demonstrate that typical dialysis and intradialytic exercise are accompanied by a moderate level of hyperthermia, which can be offset by cold dialysis. Based on these findings, we observed that hemodialysis sessions which incorporate cold dialysis alone or supplemented with intradialytic exercise can prevent the rise of body heat storage. The latter has been shown to be a major factor for developing intradialytic hypotension, which is due to both hemodynamic responses (hypovolaemia stress) and thermoregulatory responses (thermal stress) during hemodialysis.

Research Study 2

The acute effects of cold dialysis and intradialytic exercise training in parameters related to insulin sensitivity, health and fitness

Abstract

Background: Patients with end-stage renal diseases (ESRD) suffer from diabetes, hypertension, obesity, musculoskeletal problems and cardiovascular diseases, which are the main causes of mortality in these patients. It's well known that intervention such as lowering the dialysate temperature (cold dialysis; CD) and participating in various intradialytic-exercise training (IET) regimes could improve health benefits for patients undergoing hemodialysis. However, it's not known whether the combination of those two regimes could enhance overall health. The aims of the current study were to evaluate the separate and combine acute effects of a single session of CD and IET in parameters related to insulin sensitivity and hemodialysis fatigue. **Methods:** Ten ESRD patients (57.2±14.9 years) participated in the current study. Each patient was monitored during a) one session of typical dialysis with dialysate temperature at 37°C (TD), b) one session of cold dialysis with dialysate temperature at 35°C (CD), c) one session of TD combined with a single exercise bout (TD+EX), d) one session of CD combined with a single exercise bout (CD+EX). Before and after each dialysis sessions, all patients were assessed in aspects related to functional capacity, quality of life and fatigue. Insulin sensitivity was assessed after each dialysis session. **Results:** None of the four different sessions have shown any statistical significant differences ($p>0.05$). However, slightly numerical changes and moderate to high effect size (d:0.50-0.85) observed between TD vs CD and TD vs TD+EX in the rate of glucose and insulin disposal during the oral glucose tolerance test (OGTT). In addition, the systolic blood pressure observed statistically significant increased at the end of CD compared to TD. No statistical significant improvement observed in any aspect of functional capacity and fatigue parameters after an acute single session of CD and IET. **Conclusions:** A single session of CD and TD+EX may provide an "acute" time-effective stimulus for improvement of OGTT. A single session of CD could offer a better hemodynamic support to hemodialysis patients.

Keywords: cold dialysis, insulin resistance, glucose metabolism, intradialytic exercise, quality of life

Introduction

It is well recognized, that high prevalence of diabetes and cardiovascular disease are observed in patients with end-stage renal disease (ESRD)[62,169]. Uremia is typically associated with impaired glucose metabolism via multiple mechanisms[170]. Accumulation of uremic toxins may cause or contribute to insulin resistance (IR) in ESRD patients[49]. Many studies show that hemodialysis (HD) with typical dialysate temperature (TD; 37°C) can improves glucose impairment, although not completely[171]. Specifically, previous data show that, marked improvement in insulin sensitivity and glucose tolerance has been reported in nondiabetic patients with ESRD, but values did not normalize[172].

Many studies show that lowering the dialysate temperature ("cold dialysis"; CD; 35°C) may improve outcomes for patients undergoing HD. Previous studies show that "cooling" the dialysate temperature (CD; 35°C), from 37°C, which used as a typical temperature (TD) can have beneficial effects on the health and quality of life of patients with ESRD. It is well documented that CD, provide profound hemodynamic changes including a reduction in peripheral vascular resistances, elevated heart rate, cardiac output and increased muscle sympathetic nerve activity, resulting in increased blood flow to the skin and leaving the body defenseless to hypotension[12,44,154].

Also, another important factor that has been studied over the last years and appears to contribute to improving the quality of life of patients with ESRD, is physical activity and especially the intradialytic-exercise training (IET)[173]. Several of the known benefits of exercise or regular physical activity in the general population are related to areas of specific concern to patients with ESRD, such as reduced risk for cardiovascular mortality, better control of diabetes, and improvement in health-related quality of life as a result of enhanced psychologic well-being and improved physical functioning[173]. Studies in ESRD patients showed that poor physical fitness may be a contributing factor for insulin resistance (IR)[174]. Long-term exercise training in ESRD patients leading to enhanced exercise capacity and normalization of hyperglycemia and glucose intolerance[119].

However, despite the positive, long-term adaptations of CD and IET, no study, has examined the acute adaptations of these interventions. The aim of the current study was to assess the separate and combined acute effects of CD and IET in parameters related to insulin sensitivity, health and fitness in ten patients with ESRD.

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 General Hospital of Trikala, Greece. All patients gave their written informed consent prior to study participation. The study has been registered as Clinical Trial at the clinicaltrials.gov (NCT03905551)

Study Design

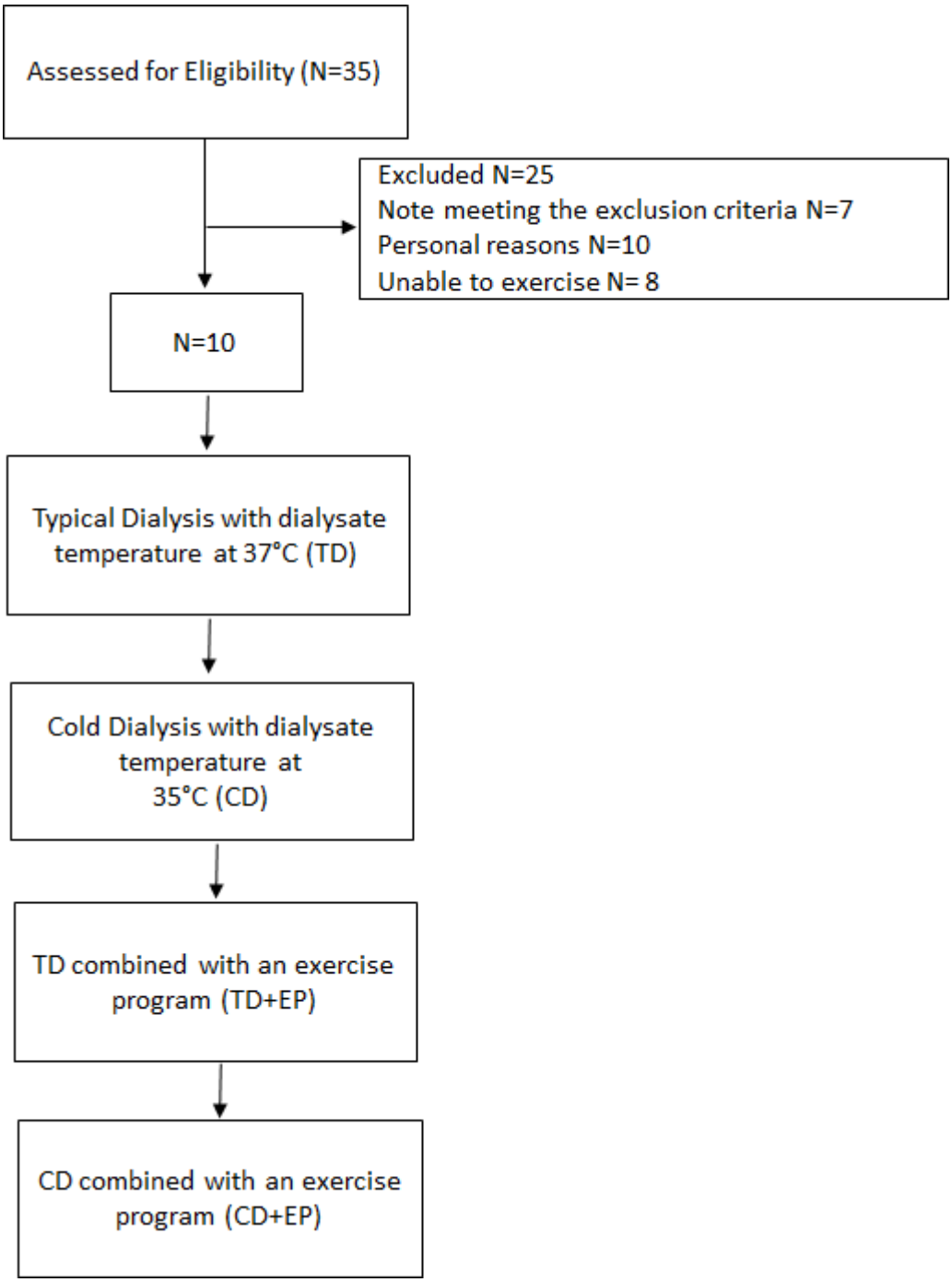
Ten haemodialysis patients (57.2±14.9 years) were selected from the haemodialysis population of the General Hospital of Trikala, Greece. The study was performed from October 2016 to June 2018. All study measurements were performed at a hospital climate control room using the metabolic ward of the General Hospital of Trikala, Greece. Patients enrolled by a research assistant assigned into the study while the order that the patients assigned to the first session was random using a computer random number generator. Each patient was monitored during a) one session of typical dialysis with dialysate temperature at 37°C (TD), b) one session of cold dialysis with dialysate temperature at 35°C (CD), c) one session of TD combined with an IET program (TD+EX), d) one session of CD combined with an IET program (CD+EX). Dialysis protocols were performed in a random order at the same time and day of the week to minimize differences in ultrafiltration volume between the four protocols. Food consumption was not allowed during the dialysis procedure. During the different dialysis protocols, arterial blood pressure, heart rate (HR), oxygen consumption (O_2), nitrogen dioxide (NO_2) and hand grip test were recorded every hour of dialysis. The data recording lasted six hours for each patient (1 hour before dialysis protocol, 4 hours during the dialysis protocol and 1 hour after dialysis protocol). The IET during TD+EX and CD+EX sessions started 1h after the commencement of the haemodialysis session. However, at the end of each dialysis protocol, all patients underwent to insulin sensitivity test, functional performance test.

Inclusion criteria: clinically stable condition, receiving regular hemodialysis treatment for at least 3 months, with adequate dialysis delivery Kt/V >1.1 and good compliance of dialysis treatment, serum albumin > 2.5 g/dL, hemoglobin ≥ 11g/dL and treatment with rHuEPO.

Exclusion criteria: reason to be in a catabolic state, such as hyperthyroidism, active vasculitis, malignancies, pregnant HIV, opportunistic infections, myoskeletical contraindication to exercise, requirement for systemic anticoagulation, participant or

participated in an investigational drug or medical device study within 30 days or five half-lives or inflammations, that required intravenous antibiotics within 3 months prior to enrollment, diabetics receiving insulin therapy, New York Heart Association grade IV heart failure, and mental incapacity to consent.

Figure 1: Flow chat of the study



Hemodialysis Procedure

The patient participants underwent hemodialysis therapy (Fresenius 4008B, Oberursel, Germany) three times per week with low flux, hollow fiber dialyzers and bicarbonate buffer. Each hemodialysis session lasted approximately 4 hours. Erythropoietin therapy (EPO) was given after the completion of HD session in order to normalize hemoglobin levels within 11–12 (g/dL).

Body Composition Assessment

The patient's whole body and regional fat and lean body mass were measured by Body Composition Monitor (BCM - Fresenius Medical Care Deutschland GmbH) which has been specifically designed for patients with kidney failure[175].

Functional Capacity Assessment

Muscle functional capacity (muscular strength and endurance) was assessed using:

1) STS-5: time to perform five sit to stand cycles, representing the level of muscle power,

2) STS-60s: number of sit to stand cycles achieved in 60 second, representing muscular endurance,

3) FWT6m: time to walk a distance of 6.00m at fast pace (fast walk) representing everyday functional capacity,

4) 6MWT: patients were instructed to cover as much distance as possible while walking for six minutes and were constantly encouraged by the researchers to increase their pace up to the level which they could barely sustain. The 6MWT performed for all of the patients on a level surface (hospital corridor) without pre-warming.

5) Hand Grip test: representing the maximum isometric strength of the hand and forearm muscles. Patients holds the dynamometer in the hand to be tested, hang their hand by their side, when are ready the patients squeezes the dynamometer with maximum isometric effort, which is maintained for about 5 seconds[14].

Insulin resistance

Insulin resistances assessed by an Oral Glucose Tolerance Test. Blood samples collected at 30, 60, 90, and 120 minutes following ingestion of the 75g glucose dissolved in 400ml of water. Insulin resistance index was calculated using the OGIS equation as previously described and validated[176].

Basal Measurements

Blood pressure, heart rate and exhaling air nitrogen dioxide, assessed before, at each hour and after HD session in both groups.

Intradialytic Exercise Training

During the intradialytic exercise training, patients performed cycling for 60 minutes in the supine position. During the sessions, the patients were asked to pedal at 45 rpm for the first 10 minutes and then to 60 rpm on a bedside cycle ergometer (https://www.youtube.com/watch?v=oiY-f38kSyY) (Model 881 Monark Rehab Trainer,Monark Exercise AB, Varberg, Sweden). Patients cycled at approximately 60% of their pre-assessed maximum power capacity. The exercise regime started 1h after the commencement of the hemodialysis session. The patients' maximum power capacity was determined by a modified version of the Åstrand Bicycle Ergometer test protocol at bedside on a previous dialysis session during hemodialysis. Exercise was well tolerated by all patients, and no adverse reactions were reported apart of some irregular muscle cramps.

Sample Size

Sample size calculations were conducted based on plasma glucose at 120 min, mg/dl in the hemodialysis patients from a previous published article[53]. The resulting minimum required sample size was 10 for 2-sided type 1 and type 2 errors 5%. Sample size calculations were conducted using G*Power 3.0.

Statistical Analysis

A Multivariate Analysis of Variance (MANOVA) followed by post-hoc paired-samples t tests were used to assess the effects of time (pre / post) and protocol (EG, CG). The MANOVA results demonstrated no statistically significant main or interaction effects. To further strengthen the analysis, Cohen's d effect sizes (0.2-0.5: small effect; 0.5-0.8: moderate effect; >0.80: large effect) were also used to identify paired differences between protocols and times. Data are expressed in mean±SD. A p value <0.05 was considered statistical significant. All analyses were carried out using the Statistical Package SPSS 21.

Results

Patient's characteristics for each dialysis session are presented in Table 1. The results presented as means average and SD. No statistically significant differences were observed among the four different sessions ($p>0.05$) (Table 1).

Table 1: Patient's characteristics for each dialysis session

Variables	TD (37°C)	CD (35°C)	TD+EX (37°C)	CD+EX (35°C)
Dry Weight	72.18±11.25	72.46±11.45	72.37±11.50	71.86±10.91
WHR	1.03±0.22	0.97±0.06	0.96±0.06	0.96±0.05
BMI	25.02±2.51	25.24±2.44	25.13±2.51	25.10±2.27
TBW	36.10±6.23	34.20±6.32	35.00±6.68	33.85±6.10
ECW	15.15±2.68	15.15±2.86	15.40±3.06	15.10±2.96
ICW	20.70±4.25	19.12±3.70	19.57±3.93	18.80±3.65
E/I	0.76±0.13	0.80±0.09	0.79±0.10	0.80±0.12
LTM	40.90±9.93	40.23±9.91	41.0±9.67	40.52±10.45
LTM %	55.96±10.73	54.9±7.88	54.84±9.13	54.7±8.72
FAT	24.0±6.50	24.9±6.62	24.09±6.80	24.48±6.52
FAT %	34.0±7.38	34.9±7.00	34.64±6.98	34.15±7.33

Note: WHR: waist hip ratio; BMI: body mass index; TBW: total body water; ECW: extracellular water; ICW: intracellular water; E/I: quotient from ECW & ICW; LTM: lean tissue mass; FAT: total lipid mass.

*** No statistical significant changes among groups**

Insulin Sensitivity results

Our findings showed no statistical significant changes after on single session of TD, CD, TD+EX and CD+EX in oral glucose tolerance test (OGTT). However, modearte to high effect size (d:0.50-0.85) observet between TD vs CD and TD vs TD+EX. In the rate of glucose and insulin disposal during oral glucose tolerance test (OGTT). Additionally, the sensitivity of the insulin as measured by OGIS index slightly increased in CD+EX session comparated with other interventions (Fig 2-4).

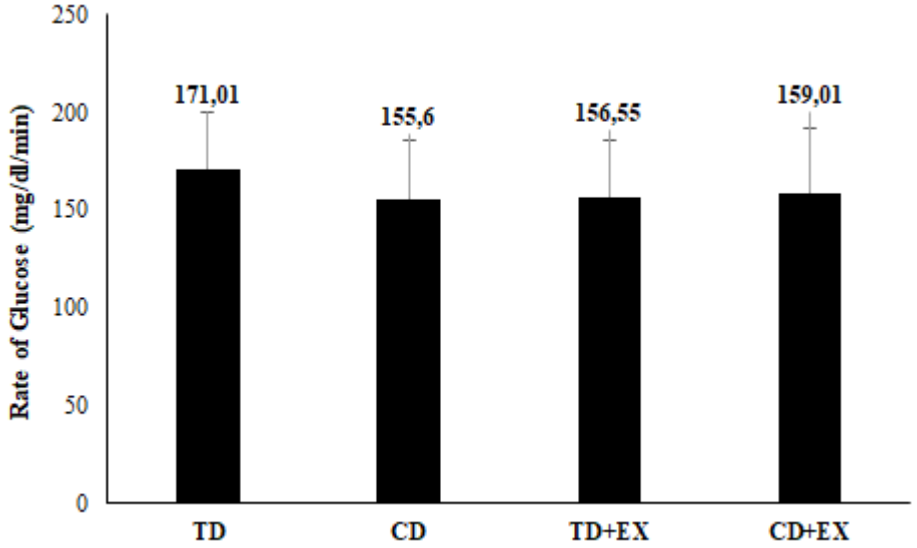


Figure 2: Rate of glucose disposal after single session of TD, CD, TD+EX, CD+EX sessions.

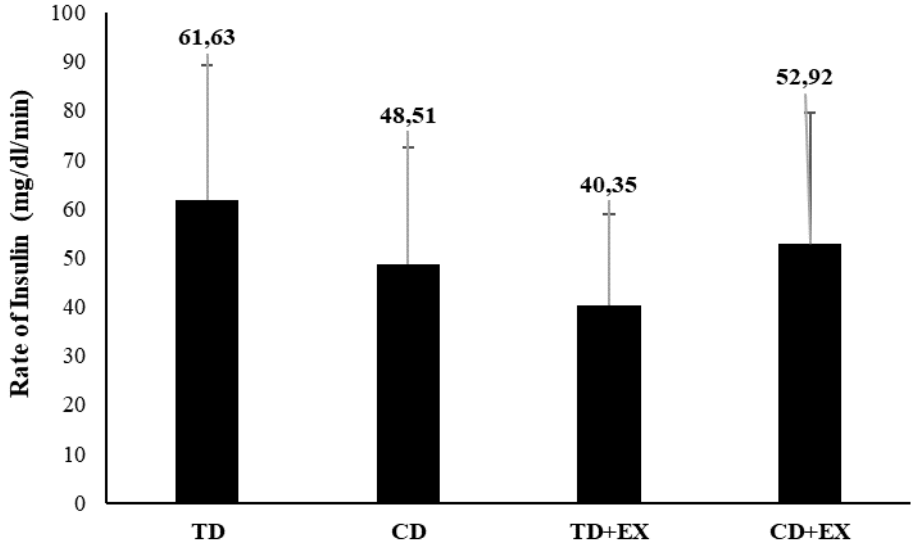


Figure 3: Rate of insulin disposal after single session of TD, CD, TD+EX, CD+EX sessions.

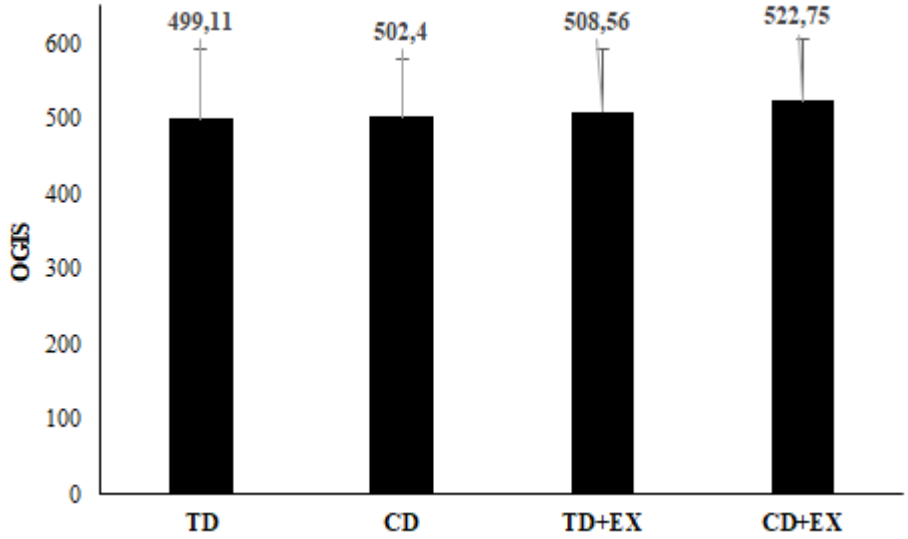


Figure 4: Insulin sensitivity as measured by OGIS index after single session of TD, CD, TD+EX, CD+EX sessions.

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Arterial pressure, No_2, Heart Rate

The systolic blood pressure statistically significant ($p<0.05$) increased at the end of CD session compared to TD and CD+EX sessions (TD: 120.1±25.5mmHg; CD: 130.0±31.3mmHg; CD+EX: 118.7±31.4mmHg) (Fig 5).

On the other hand, diastolic blood pressure showed a statistically significant increased ($p<0.05$, $p=0.01$) during the 4th hour of CD session compared to TD session (TD: 66.7±9.2; CD: 74.2±12.7).

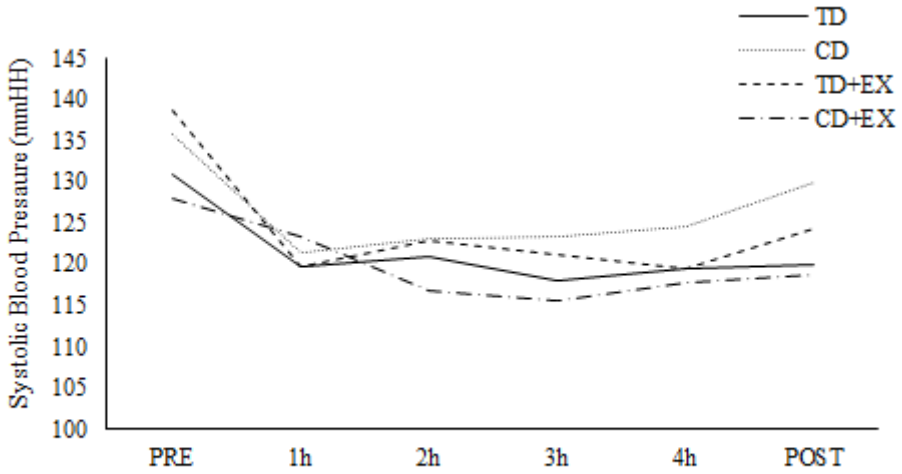


Figure 5: Changes in systolic blood pressure before, during and after single session of TD, CD, TD+EX, CD+EX sessions.

Functional Capacity

No statistical significant differences were observed in the six minute walking test, six meter fast walking, STS-5 repetitions and STS-60 seconds among sessions ($p>0.05$) However positive numerical changes observed after a single session of CD, and TD+EX in functional test (Fig 6-9). However, after CD session, handgrip strength statistically significant increased ($p<0.05$, $p=0.03$) compared to TD session (Fig 10).

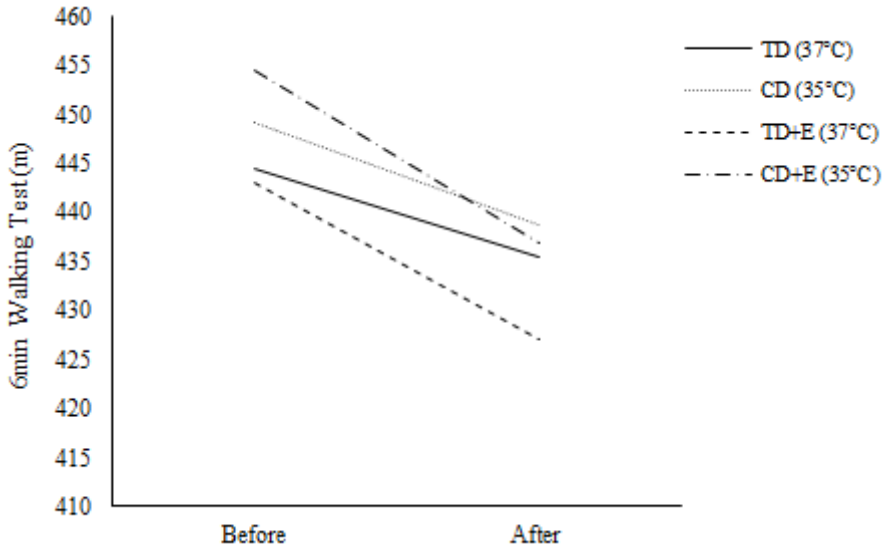


Figure 6: Six-minute walking test before and after a single session of TD, CD, TD+EX, CD+EX sessions.

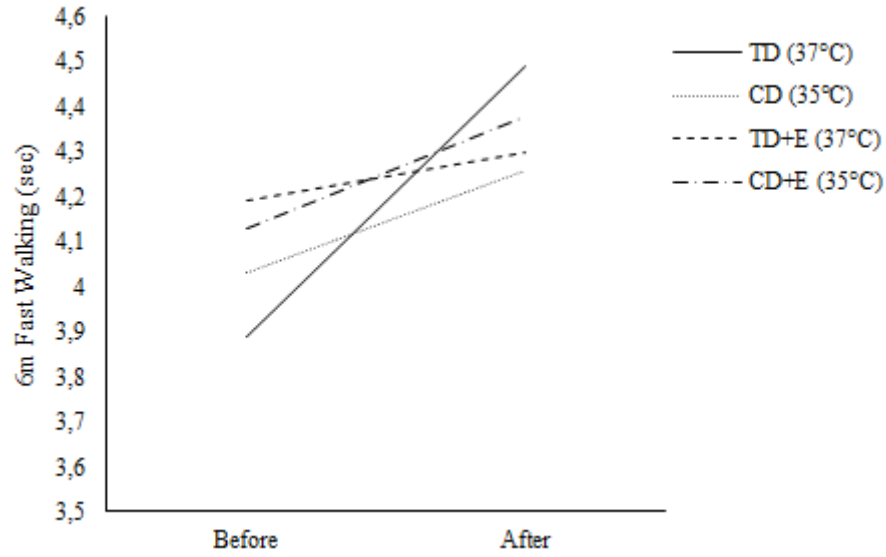


Figure 7: Six-meter fast walking test before and after a single session of TD, CD, TD+EX, CD+EX sessions.

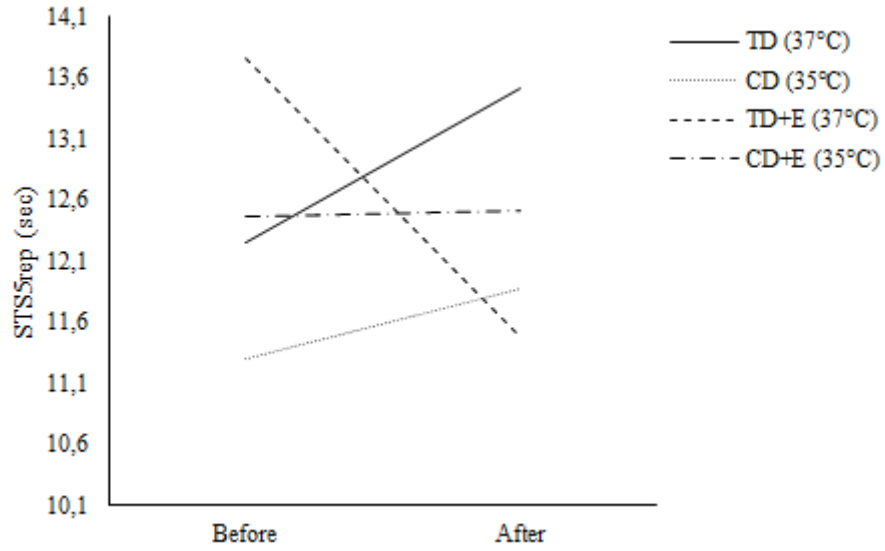


Figure 8: Sit to stand 5 repetitions test before and after a single session of TD, CD, TD+EX, CD+EX sessions.

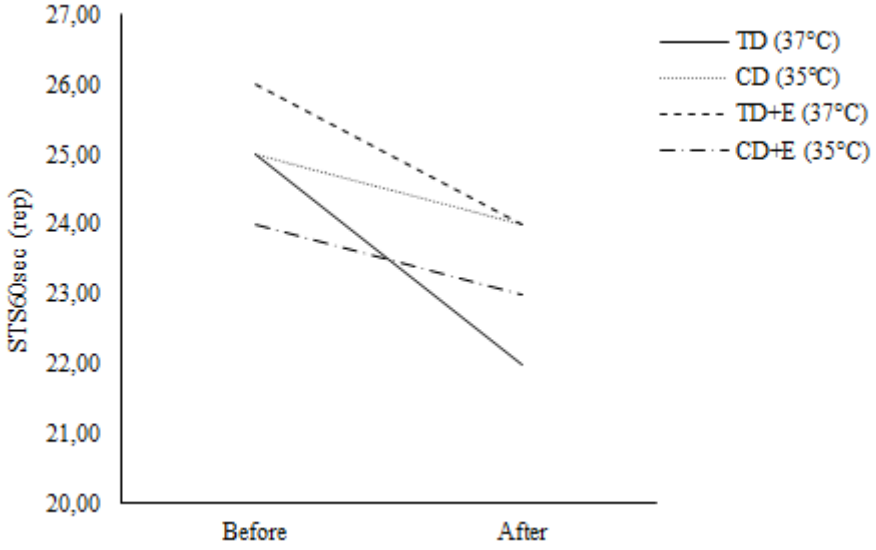


Figure 9: Sit to stand 60 seconds test before and after a single session of TD, CD, TD+EX, CD+EX sessions.

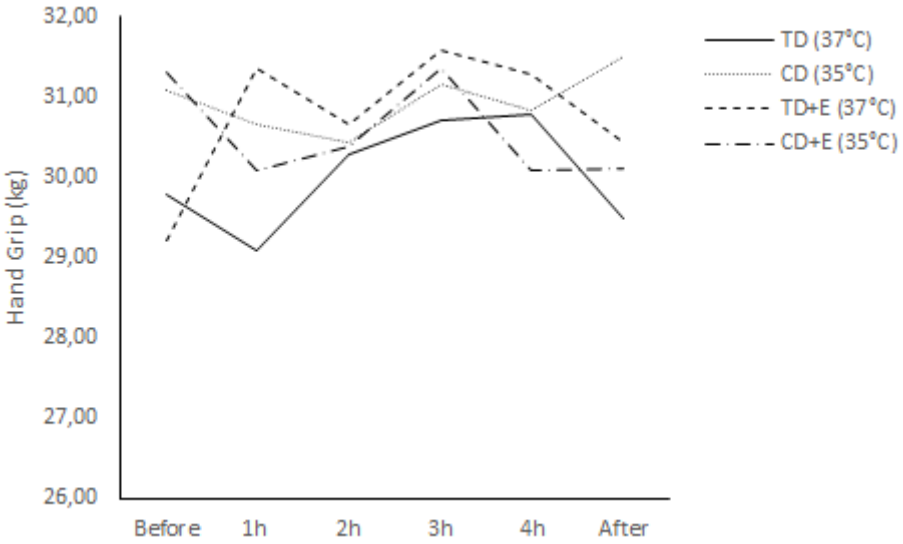


Figure 10: Hand grip test before and after a single session of TD, CD, TD+EX, CD+EX sessions.

Discussion

The present study, sought to examine for the first time the separate and combined effects of cold dialysis and intradialytic exercise training on parameters related to glucose disposal, health and fitness in hemodialysis patients. Our results demonstrated that one session of cold dialysis, associate with improvements in insulin sensitivity and systolic blood pressure compared to typical dialysis.

It well know that intradialytic exercise training is beneficial for patient with ESRD[177]. Specifically, the adaptations suggest that exercise may ameliorate muscle catabolism by promoting an anabolic milieu, thereby potentially improving the clinical sequelae of sarcopenia, such as muscle weakness, falls, fractures, frailty, insulin resistance, and immune dysfunction, in ESRD patients[14]. Also, studies showed that CD contributes to the secretion of endorphins which promote better consumption of glucose from the peripheral tissues[12]. In additional, there is a hypothesis that, since exposure to cold activates brown adipose tissue, the benefits of CD may be related to this effect. Brown adipose tissue affects whole-body metabolism, is essential for thermogenesis in human neonates and may regulate susceptibility to weight gain and insulin sensitivity[68].

Another important finding of the present study, is that once again, confirmed the positive effect of CD on maintaining blood pressure. Our results showed better preservation of systolic blood pressure at the end of CD dialysis protocol (Table 3). Studies showed that the rate of intradialytic hypotension was reduced by 70% with CD compared with TD.[9]

In addition, the present study showed that fatigue did not improve among the different sessions (Table 4-Table 5). Several studies have examined the separate effects of intradialytic exercise training and cold dialysis in patient's quality of life[14,154]. Our results showed that TD+EX session provided, moderate effect of the acute levels of fatigue compared to the others dialysis sessions (Table 5). Previous studies showed that, improvement perceptions of ‘physical functioning,’ have been observed secondary to 3–5 months of aerobic exercise[138]. DePaul et al. (2002) showed that one trial didn’t improved any parameters of patient's quality of life[141]. The lack of statistical significance between sessions could be due to the fact that our patients had high functional status at baseline of the study. However, Selby et al (2006) reported that there was no difference between CD and TD in patient’s quality of life[154].

In conclusion, the present study tried for the first time to examine the separate and combined acute effects of cold dialysis and intradialytic exercise training. A single session

of CD combined with a 60 min IET provided an “acute” time-effective stimulus for improvement in insulin sensitivity and blood pressure. However, changes in parameters related to quality of life and fatigue may require longer and more intense training regimes. The small sample size that evaluated in this study, may is the most likely cause, that no clear direction has been observed in our results. Further research is required, to examine the separate and combine acute effects of CD and IE.

Conclusions: A single session of CD and TD+EX may provide an “acute” time-effective stimulus for improvement of OGTT. A single session of CD could offer a better hemodynamic support to hemodialysis patients.

Research Study 3

Cold dialysis enhances exercise stimulus in maintaining glucose homeostasis in stable hemodialysis patients

Abstract

Background: Hemodialysis (HD) patients suffer for severe insulin resistance, which contributes to the pathogenesis of atherosclerotic cardiovascular disease, often seen in chronic uremia, and is associated with enhanced morbidity and mortality. The cold dialysis (CD) appears to impose a positive impact on cardiovascular health of HD patients. Intradialytic exercise training (IET) provides numerous health-related benefits derived from engaging in appropriately structured exercise programs. However, it is unknown whether the combination of CD and IET has a synergistic effect on enhancing exercise performance and improving insulin resistance. The aim of the current study was to assess the effects of IET in combination with CD in parameters related to insulin resistance and exercise capacity in HD patients after 7 months of supervised exercise training.

Methods: Fourteen stable HD patients participated in the current study and randomly allocated in one of the two groups: the Cold Dialysis (35°C) + Exercise Group (N=7) (CD+EX) which received 7 -months of IET combined with low dialysate temperature and the Typical Dialysis (TD) (37°C)+Exercise Group (N=7) (TD+EX) which received 7-months of IET combined with typical dialysate temperature. All patients assessed for aspects related to body composition, functional capacity and insulin resistance before and after the exercise intervention.

Results: Insulin sensitivity index was improved by 32% in CD+EX group compared to TD+EX group. In addition, rate of glucose and insulin disposal during OGTT was improved in CD+EX group compered to TD+EX group. Functional capacity and indices of quality of life improved in both groups ($P<0.05$) independent of dialysate temperature.

Conclusion: Reduction of dialysate temperature by 2°C induced favorable changes in aspects related to insulin sensitivity and glucose disposal. Cold dialysis, also improved hemodynamic changes, occurring during dialysis reducing thus possible hypotension symptoms. Exercise training improved overall exercise capacity and indices of quality of life, irrespective dialysate temperature. Cold dialysis and Intradialytic exercise training enhances health benefits improving overall patients' quality of life.

Keywords: cold dialysis, insulin resistance, glucose metabolism, intradialytic exercise, quality of life

Introduction

Abnormal glycemic control is a common feature in patients with end stage renal disease (ESRD) that is often associated with high morbidity and mortality[178]. In the 1980s, DeFronzo et al (1981) using the 'gold standard' euglycemic hyperinsulinemic clamp technique, found evidence of insulin resistance (IR) in ESRD patients[55]. IR is characterized by resistance to the effects of insulin on glucose uptake, metabolism or storage. This effect is manifested by decreased insulin-stimulated glucose transport and metabolism in adipocytes and skeletal muscle and by impaired suppression of hepatic glucose output[49]. Many factors have been implicated in the pathogenesis of increased IR including anemia, physical inactivity, uremic myopathy and numerous potential uremic toxins, particularly of the middle molecule variety, these factors leading to the reduction of quality life in ESRD patients[55,179].

Hemodialysis (HD) is a life-saving replacement therapy, however, many studies have shown that IR is a prominent characteristic in most pre-dialysis nondiabetic patients with ESRD[172]. In addition improvements in insulin sensitivity and glucose tolerance has been reported in nondiabetic ESRD patients after the initiation of HD, although values did not normalize to those in healthy individuals[171]. In addition, many HD patients develop IR and diabetes after a few years of HD as a result of the accumulated chronic toxicity[180]. This is compatible with hypothesis that inadequate dialysis and circulating uremic toxins could play a pivotal role in IR in uremia[181].

Lowering the dialysate temperature (35-36°C; cold dialysis; CD) has been proposed as a simple and useful method to improve many aspects of health, in patients undergoing HD[9]. The CD has been employed as a countermeasure to reduce intradialytic hypotension episodes, by increasing peripheral resistance leading to increased intradialytic mean arterial pressure without jeopardizing dialysis adequacy[182]. In addition, there is accumulated evidence to suggest that CD can also reduce overall cardiovascular mortality[45]. In general, ESRD patients tolerate long term CD very well, reporting high levels of satisfaction (76%-80%), less fatigue, faster recovery times after dialysis, feeling more energetic, with better cognitive capacity and having the overall sensation that their general health has dramatically improved[154].

Intradialytic exercise training (IET) also provides numerous health-related benefits derived from engaging in appropriately structured exercise programs[183]. The rationale for prescribing exercise in this patient population is extremely strong[184]. Moreover, regular physical exercise can ameliorate several cardiovascular decrease risk factors thus reducing,

cardiovascular morbidity and mortality, which are very high in dialysis patients[174]. Also IET has been shown to have benefits on the dialysis efficacy, physical function and health-related quality of life[173]. As we mentioned above IR is a characteristic feature of uremia, irrespective of the type of renal disease, with muscle tissue insensitivity being the primary cause. Previous evidence show that physical exercise improves insulin sensitivity in both normal individuals and patients with lifestyle-related diseases[185].

Despite a strong rationale for the implementation of intradialytic exercise training programs and the aforementioned benefits of CD, the combined effects of IET and CD have not been investigated to date.

The aim of the current study was to assess the effects of IET and CD in parameters related to insulin resistance and overall quality of life in patients with ESRD after 7 months of aerobic exercise training.

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 General Hospital of Trikala, Greece. All patients gave their written informed consent prior to study participation. The study has been registered as Clinical Trial at the clinicaltrials.gov (NCT03905551).

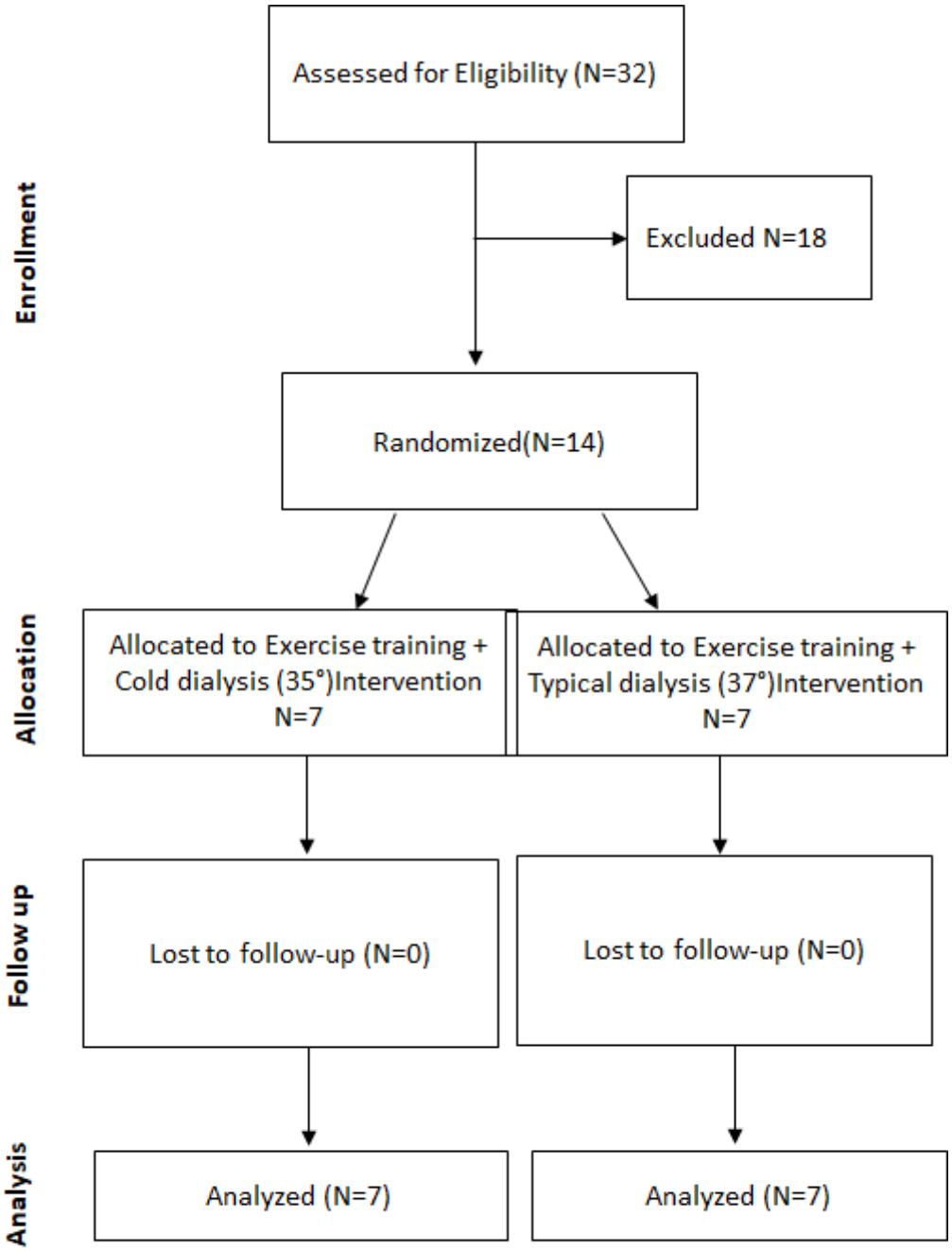
Study Population

Fourteen haemodialysis patients participated in this study. Inclusion criteria: clinically stable condition, receiving regular hemodialysis treatment for at least 3 months, with adequate dialysis delivery Kt/V >1.1 and good compliance of dialysis treatment, serum albumin > 2.5 g/dL, hemoglobin ≥ 11g/dL and treatment with rHuEPO. Exclusion criteria: reason to be in a catabolic state, such as hyperthyroidism, active vasculitis, malignancies, pregnant HIV, opportunistic infections, myoskeletical contraindication to exercise, requirement for systemic anticoagulation, participant or participated in an investigational drug or medical device study within 30 days or five half-lives or inflammations, that required intravenous antibiotics within 3 months prior to enrollment, diabetics receiving insulin therapy, New York Heart Association grade IV heart failure, and mental incapacity to consent.

Study Design

Patients recruited from the hemodialysis unit of General Hospital Trikala, Greece and the Eftychios Patsides General Clinic, Larisa, Greece. The study was performed from October 2016 to July 2018. All participants received 7 months of supervised intradialytic aerobic exercise training. Patients were randomized by a randomization software and assigned in two groups: the Cold Dialysis (35°C) + Exercise Group (N=7) (CD+EX) and the Typical Dialysis (37°C) + Exercise Group (N=7) (TD+EX). All patients assessed for their body composition, functional capacity, blood pressure and insulin resistance. Quality of life and fatigue severity were assessed by validated questionnaires. All measurements took place immediately after the cessation of the HD session and before and after the 7 months experimental intervention.

Figure 1: Study design flow chart.



Hemodialysis Procedure

The patient participants underwent hemodialysis therapy (Fresenius 4008B, Oberursel, Germany) three times per week with low flux, hollow fiber dialyzers and bicarbonate

buffer. Each hemodialysis session lasted approximately 4 hours. Erythropoietin therapy (EPO) was given after the completion of HD session in order to normalize hemoglobin levels within 11–12 (g/dL).

Body Composition Assessment

The patient's whole body and regional fat and lean body mass were measured by Body Composition Monitor (BCM - Fresenius Medical Care Deutschland GmbH) which has been specifically designed for patients with kidney failure[186].

Functional Capacity Assessment

Muscle functional capacity (muscular strength and endurance) was assessed using:

1) STS-5: time to perform five sit to stand cycles, representing the level of muscle power,

2) STS-60s: number of sit to stand cycles achieved in 60 second, representing muscular endurance,

3) FWT6m: time to walk a distance of 6.00m at fast pace (fast walk) representing everyday functional capacity,

4) 6MWT: patients were instructed to cover as much distance as possible while walking for six minutes and were constantly encouraged by the researchers to increase their pace up to the level which they could barely sustain. The 6MWT performed for all of the patients on a level surface (hospital corridor) without pre-warming.

5) Hand Grip test: representing the maximum isometric strength of the hand and forearm muscles. Patients holds the dynamometer in the hand to be tested, hang their hand by their side, when are ready the patients squeezes the dynamometer with maximum isometric effort, which is maintained for about 5 seconds[187,188].

Questionnaires

QoL was assessed by using the SF36 QoL questionnaire adjusted and validated in dialysis patients. Fatigue Severity was assessed by using Fatigue Severity Scale. All questionnaires were administrated and supervised by an experienced personnel using the interview method[189,190].

Insulin resistance

Insulin resistances assessed by an Oral Glucose Tolerance Test. Blood samples collected at 30, 60, 90, and 120 minutes following ingestion of the 75g glucose dissolved in 400ml of

water. Insulin resistance index was calculated using the OGIS equation as previously described and validated[191].

Basal Measurements

Blood pressure, heart rate and exhaling air nitrogen dioxide, assessed before, at each hour and after HD session in both groups.

Biochemical Analysis

Albumin, hemoglobin (Hb), and hematocrit (Hct) blood analyses were performed at the hemodialysis clinical laboratory of the General Hospital of Trikala under standard hospital procedures.

Physical Activity Assessment

Physical activity was measured by using pedometer (Digi-Walker, SW-200 pedometer), which was given to each participant. Participants were instructed to attach the pedometer at the waistline each morning and to wear the pedometer throughout the day while doing usual activities, except during bathing. They were asked to remove the pedometer before going to bed and to record the day's step count each night before resetting the device to zero for the next day. Physical activity recorder, was held one week (7 days) before the experimental intervention started and one week (7 days) after the completion of the experimental intervention.

Intradialytic Exercise Training

During the intradialytic exercise training, patients performed cycling for 60 minutes in the supine position. During the sessions, the patients were asked to pedal at 45 rpm for the first 10 minutes and then to 60 rpm on a bedside cycle ergometer (https://www.youtube.com/watch?v=oiY-f38kSyY) (Model 881 Monark Rehab Trainer,Monark Exercise AB, Varberg, Sweden). Patients cycled at approximately 60% of their pre-assessed maximum power capacity. The exercise regime started 1h after the commencement of the hemodialysis session. The patients' maximum power capacity was determined by a modified version of the Åstrand Bicycle Ergometer test protocol at bedside on a previous dialysis session during hemodialysis. Exercise was well tolerated by all patients, and no adverse reactions were reported apart of some irregular muscle cramps.

Sample Size

Sample size calculations were conducted based on plasma glucose at 120 min, mg/dl in the hemodialysis patients from a previous published article[180]. The resulting minimum required sample size was 6 for 2-sided type 1 and type 2 errors 5%. Sample size calculations were conducted using G*Power 3.0.

Statistical Analysis

A Multivariate Analysis of Variance (MANOVA) followed by post-hoc paired-samples t tests were used to assess the effects of time (pre / post) and protocol (EG, CG). The MANOVA results demonstrated no statistically significant main or interaction effects. To further strengthen the analysis, Cohen's d effect sizes (0.2-0.5: small effect; 0.5-0.8: moderate effect; >0.80: large effect) were also used to identify paired differences between protocols and times. Data expressed as mean±SD. A p value <0.05 was considered statistical significant. All analyses were carried out using the Statistical Package SPSS 21.

Result

Characteristics of the study population are presented in Table 1. Briefly, 14 stable haemodialysis patients (10 men/4 women), fulfilled the eligibility criteria and participated in the study.

Table 1: Patient's characteristics according to study allocation

Variables	**CD+EX**	**TD+EX**
N	7	7
Male/Female	7/0	3/4
Age (yr)	63.57±9.93	52.71±16.84
Dry Weight (kg)	75.86±7.45	63.65±13.13
Height (cm)	172.8±7.40	167.1±5.76
BMI (kg/m^2)	25.54±2.48	22.80±4.17
WHR	0.97	1.02
TBW	38.30	31.31
ECW	16.77	14.07
ICW	21.51	17.22
E/I	0.80	0.82
LTM (kg)	58.78	55.78
FAT(kg)	24.48	30.65
Years in Hemodialysis	8.14±2.90	8.71±3.10
Hct	35.58±3.02	35.94±2.91
Hb (g/dl)	11.14±1.14	11.56±0.71
Albumin (g/dl)	4.17±0.15	4.28±0.36

Note: All data are mean ± SD. Abbreviations: BMI, Body mass index; WHR, waist hip-ratio; TBW, total body water; ECW, extracellular water, ICW, intracellular water; E/I, extracellular- intracellular water ratio; LTM, lean total mass; Hct, Hematocrit; Hb, Hemoglobin.

Our findings showed that the rate of glucose and insulin disposal during oral glucose tolerance test (OGTT) was improved in CD+EX group compared to TD+EX group after 7 months of intervention ($p<0.05$, $d>0.80$). More specifically, the insulin sensitivity index (OGIS) was improved by 32% in CD+EX group compared to TD+EX group (Fig 2).

Table 2. Insulin sensitivity indices according to study allocation.

Variables	CD+EX	TD+EX
OGIS		
Baseline	504.29±90.47	622.43±113.12
7-m post	588.86±191.59	476.14±103.72
Δ Change (%)	16.77±111.77	-23.50±-8.31
P value	0.38	**0.00**
Effect size	0.49	1.16
Rate of Glucose disposal (mg/dl/min)		
Baseline	160.59±31.25	137.48±36.54
7-m post	103.43±15.81	124.84±26.58
Δ Change (%)	-35.59±-49.40	-9.19±-27.27
P value	**0.00**	0.30
Effect size	1.99	0.34
Rate of Insulin disposal (mg/dl/min)		
Baseline	59.06±17.73	39.46±33.03
7-m post	21.03±8.38	41.39±17.25
Δ Change (%)	-183.47±54.47	16.46±58.84
P value	**0.00**	0.86
Effect size	**2.42**	0.07

Note: Cohen's d, d=0.20-0.50 small, d=0.50-0.80 moderate, d>0.80 large effect size; Significance level P<0.05.

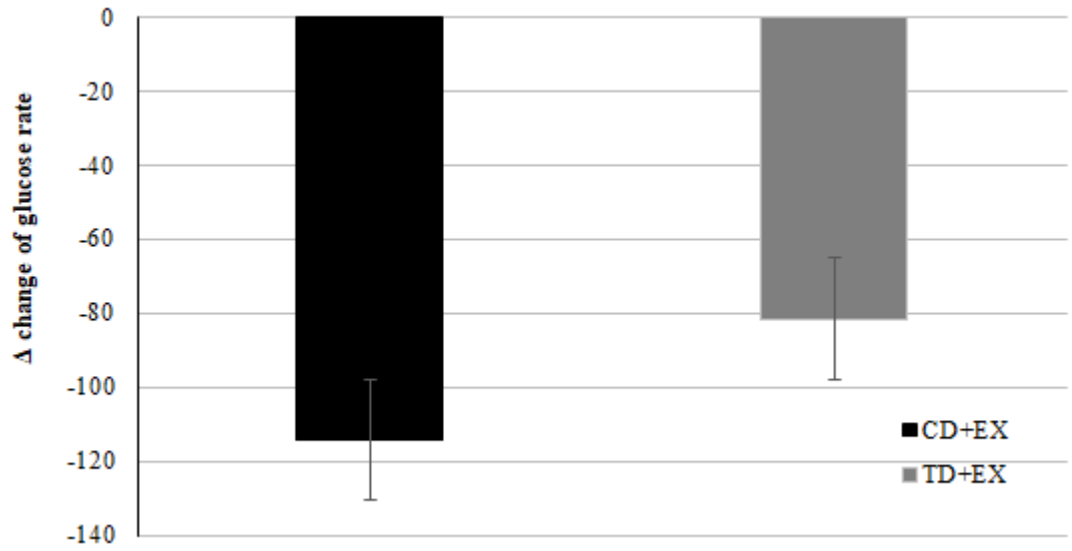


Figure 2: The insulin sensitivity index (OGIS) was improved by 32% in CD+EX group compared to TD+EX group.

In addition, systolic blood pressure as assessed after the hemodialysis session improved statistically significant in CD+EX group (p=0.05) compared to TD+EX (Table 3).

Table 3. Blood pressure, nitrogen dioxide and heart rate data according to study allocation.

Variables	CD+EX	TD+EX
Systolic Pressure (mmHg)		
Baseline	127.29±21.38	121.71±22.45
7-m post	137.29±20.14	126.71±18.17
Δ Change (%)	7.85±-5.79	4.10±-19.05
P value	**0.05**	0.30
Effect size	0.45	0.23
Diastolic Pressure (mmHg)		
Baseline	73.43±12.82	69.29±10.31
7-m post	75.29±12.72	66.43±11.96
Δ Change (%)	2.53±-0.71	-4.12±16.07
P value	0.72	0.59
Effect size	0.14	0.18
NO_2 (parts per billion)		
Baseline	8.71±2.62	5.86±6.23
7-m post	6.43±4.15	5.00±4.96
Δ Change (%)	-26.22±58.22	-14.63±-20.27
P value	0.28	0.78
Effect size	0.61	0.14
Heart Rate* (BPM)		
Baseline	68.86±18.21	79.00±13.67
7-m post	73.00±10.95	71.71±9.14
Δ Change (%)	6.01±-39.86	-9.22±-33.14
P value	0.38	0.13
Effect size	0.26	0.58

Note: Cohen's d, d=0.20-0.50 small, d=0.50-0.80 moderate, d>0.80 large effect size; Significance level P<0.05.

***** Heart rate was assessed prior to the initiation of the HD session

Functional capacity improved in both groups after 7 months of intervention, independently of dialysate temperature (Table 4). Specifically, STS-60sec as well as the 6min walking distance was increased statistically in both groups (p<0.05). Regarding STS5rep, 6-meter fast walking test and hand grip observed slightly improvement after 7 months of intervention in both groups, however this improvement did not reach the statistical significant level (Table 4). Physical activity levels tend to improve in both groups (CD+EX; p=0.06 vs TD+EX; p=0.07) after 7 months of intervention.

Table 4. Functional capacity according to study allocation.

Variables	CD+EX	TD+EX
STS-5 (min)		
Baseline	13.23±7.16	12.20±7.45
7-m post	12.45±7.22	10.66±7.81
Δ Change (%)	-5.86±0.78	-12.58
P value	0.35	0.22
Effect size	0.10	0.19
STS-60 (rep)		
Baseline	23.43±8.50	26.43±5.94
7-m post	27.43±9.67	31.00±8.26
Δ Change (%)	17.07±13.80	17.29±39.16
P value	**0.05**	**0.02**
Effect size	0.41	0.59
6m Fast Walk (sec)		
Baseline	4.45±0.91	3.63±1.58
7-m post	3.96±0.77	3.36±1.16
Δ Change (%)	-10.99±-14.60	-7.31±-26.46
P value	0.18	0.45
Effect size	0.54	0.18
6min Walk Test (m)		
Baseline	376.86±112.59	389.14±124.52
7-m post	416.57±104.44	424.14±117.70
Δ Change (%)	10.53±-7.24	8.99±-5.46
P value	**0.01**	**0.02**
Effect size	0.34	0.27
Hand Grip (kg)		
Baseline	29.52±6.76	27.15±7.85
7-m post	31.29±7.80	28.48±9.64
Δ Change (%)	5.97±15.34	4.89±22.81
P value	0.08	0.18
Effect size	0.23	0.14
Max test (watt)		
Baseline	35.71±9.75	32.86±14.96
7-m post	44.29±15.11	42.86±24.30
Δ Change (%)	24.0±54.91	30.43±62.42
P value	0.08	**0.04**
Effect size	0.63	0.46
Physical Activity (steps per day)		
Baseline	5589±1204	4926±1718
7-m post	6420±7619	5665±2130
Δ Change (%)	12.9±58.1	13.0±19.3
P value	0.06	0.07
Effect size	0.15	0.38

Note: STS-5: five sit to stand cycles; STS-60: sit to stand cycles in 60 second; Cohen's d, d=0.20-0.50 small, d=0.50-0.80 moderate, d>0.80 large effect size; Significance level P<0.05.

Quality of life improved in both group while fatigue changes did not reach the statistical significant level (Table 5).

Table 5. Aspects of Quality of life according to study allocation.

Variables	CD+EX				TD+EX			
	Pre	Post	P values	Effect size	Pre	Post	P values	Effect size
SF-36 Quality of Life								
Physical Function	75.71±29.08	84.29±22.11	0.13	0.29	89.29±18.41	92.14±15.32	0.10	0.14
Role Function	90.00±10.35	95.00±8.86	0.21	0.45	96.43±8.75	98.57±3.50	0.35	0.28
Body Pain	94.29±7.28	93.33±9.43	1.00	0.00	94.86±8.20	97.71±5.60	0.35	0.35
General Health	71.57±12.13	76.71±16.27	0.24	0.31	66.14±14.53	80.29±13.38	**0.01**	**0.87**
Vitality	92.86±13.59	95.71±8.63	0.23	0.22	78.57±16.41	96.43±5.15	**0.03**	**1.26**
Role Emotional	93.14±11.86	95.71±6.78	0.35	0.23	90.57±14.91	93.14±11.86	0.35	0.16
Mental Health	77.71±5.60	80.00±4.66	0.40	0.38	73.14±5.11	78.71±3.81	**0.05**	**1.06**
Physical Health	81.43±10.38	86.00±11.46	0.11	0.36	84.00±10.43	92.14±6.38	**0.00**	**0.81**
Mental Health	85.29±3.53	87.29±3.41	0.22	0.50	81.43±6.21	88.57±4.92	**0.00**	**1.10**
Total	87.57±6.09	93.00±3.21	**0.00**	**0.96**	86.14±7.40	92.43±5.45	**0.00**	**0.83**
Fatigue Severity Scale								
FSS	3.09±1.06	2.97±0.90	0.30	0.10	3.69±0.99	3.61±0.93	0.42	0.07

Discussion

The present study, sought to assess the chronic effects of CD combined with the IET in parameters related to insulin resistance and exercise capacity of patients with end stage renal disease (ESRD) after seven months of intervention. The current results suggest that CD seems to enhance the IET effect on health and provides a time-effective stimulus for improving insulin resistance in ESRD patients. As expected, exercise training improved overall exercise capacity and indices of quality of life in both groups, irrespective dialysate temperature.

It well established that, glucose intolerance in patients with ESRD associated with insulin resistance in peripheral tissues such as skeletal muscles and adipose tissue[49,192]. In addition, previous studies have indicated that hemodialysis *per se* is capable of improving carbohydrate metabolism in chronic uremia, by the amelioration of glucose intolerance in association with an increase in tissue sensitivity to insulin[62]. The mechanism of the improvement in the glucose tolerance and insulin resistance of uremic patients after the initiation of the hemodialysis treatment has not been well established, however, it seems that chronic uremic toxicity enhances insulin resistant where eventually leads to diabetes[180].

Cooling the dialysate temperature improves hemodynamic tolerability of hemodialysis and exerts a protective effect over major organs[9]. In a previous study from our group assessing core and skin temperatures using an ingestible telemetric pill and wireless skin sensors, we found that CD prevented the rise in body heat storage and core temperature and improved overall hypovolemic stress. However, there are sporadic reports in the literature as well as anecdotal reports about the effect of cooling/reducing body temperature in insulin resistance[193]. Recent findings document that cold exposure activates BAT via adrenergic stimulation, which combusts significant amounts of blood glucose and free fatty acid (FFA) to produce heat[194]. Many studies suggest that BAT activation improves insulin sensitivity[195]. The investigators' central hypothesis is that cold-induced BAT activation increases whole body insulin sensitivity in humans via augmented plasma glucose and FFA clearance[196]. Also, stimulation of energy expenditure by cold exposure or exercise training generally leads to decreased plasma insulin levels and to an improvement in glucose tolerance, suggesting that insulin action on peripheral tissues increased when energy expenditure is stimulated[197]. Based on the above, we hypothesized that, cooling the dialysate temperature could improve insulin sensitivity in patients with ESRD. Indeed, our results showed a 20% improvement in OGIS and 32% in glucose metabolism in CD+EX group compared with TD+EX group due to a potential increase in glucose uptake in

peripheral tissues primarily by enhancing glucose oxidation via insulin-independent pathways, and secondarily by increasing the responsiveness of peripheral tissues to insulin. On the other hand, a colder dialysate solution may induce an activation to the sympathetic nervous system and BAT metabolism, resulting an improvement in glucose metabolism without affecting pancreatic insulin secretion[194]. However, since those mechanisms have not been appropriately assessed in the current study, our data need to be viewed with caution and seek further validation in future studies.

Many studies showed the beneficial effects of cold dialysis (CD) in patients' health. Specifically lowering the dialysate temperature from 37°C to the 35°C leads to a lowering body core temperature which is improve systemic vascular resistance and therefore improve hemodynamic stability, which is a very promising approach for the prevention of intradialytic hypotension[154]. Other physiological adaptations of CD include reduction in heart rate, cardiac output and stroke volume leading to high arterial blood pressure maintaining thus a greater total peripheral resistance after hemodialysis. Mustafa et al (2015) showed that the rate of intradialytic hypotension was reduced by 70% with CD compared with typical dialysis (TD; 37°C)[8]. Also the available evidence suggests no negative effect on dialysis adequacy, with an increase in symptoms of discomfort of unclear severity during CD. In general, ESRD patients receiving CD hemodialysis, reporting high levels of satisfaction (76%-80%), less fatigue, faster recovery times after dialysis, feeling more energetic, with better cognitive capacity and having the overall sensation that their general health has dramatically improved[9].

The present results confirm previous studies that examined the effect of intradialytic exercise training in exercise capacity and quality of life. Both groups presented a significant improvement in aspects related to exercise capacity and quality of life. It is widely accepted that exercise is beneficial in patients with ESRD as in the general population while aerobic exercise exerts a beneficial role not only in improving physical functioning, muscular strength and endurance but also and in health-related quality of life.

The reduction of arterial blood pressure at the end of the haemodialysis session is an another aspect of an independent risk factor for cardiovascular mortality in ESRD patients and significantly affects patients post dialysis energy levels and overall quality of life[153]. Our results showed clinical improvements in systolic blood pressure in post dialysis hours in CD+EX group compared to TD+EX group (Table 3 $p<0.05$). Cold dialysis is a very promising approach for the prevention of intradialytic hypotension with many studies reporting improvements in hemodynamic stability including reduction in heart rate, cardiac

output and stroke volume leading to high arterial blood pressure maintaining thus a greater total peripheral resistance.

Despite the positive results of cold dialysis which have been reported in the recent literature the lack of long term interventions and properly designed randomized clinical trials justifies the modest implementation of cold dialysis.

Conclusion

This is the first clinical trial showing that cold dialysis in combination with supervised intradialytic aerobic exercise training improved insulin sensitivity index by 20% and the rate of glucose disposal by 32% compared to the typical dialysis group. The reduction of dialysate temperature by 2°C induced favorable changes in aspects related to insulin sensitivity and glucose disposal while induced favorable changes on the hemodynamic response to dialysis. Cold dialysis seems to enhance exercise-induced health benefits in ESRD patients receiving hemodialysis therapy.

Research Study 4

7 months of aerobic intradialytic exercise training, may preserve indices of muscle cachexia: an ultrasonography study

Under Review**:** 7 months of aerobic intradialytic exercise training, may preserve indices of muscle cachexia: an ultrasonography study. **A.A Krase**, G. Terzis, A.D. Flouris, A.N Stasinaki, I. Stefanidis, N. Tsianas, P. Founta, E. Patrikalou, E. Lavdas, CD Giannaki, C. Karatzaferi, G.K. Sakkas. Submitted in American Journal of Kidney Diseases 2019

Abstract

Objectives: This study aimed to evaluate the effects of cold dialysis and 7-month of intradialytic exercise training (IET) on changes in vastus lateralis (VL) muscle architecture, functional capacity and quality of life in hemodialysis (HD) patients.

Methods: Fourteen stable HD patients participated in the current study and randomly allocated in one of the two groups: the Cold Dialysis (35°C) + Exercise Group (N=7) (CD+EX) which received a 7-month IET combined with low dialysate temperature and the Typical Dialysis (TD) (37°C)+Exercise Group (N=7) (TD+EX) which received a 7-month IET combined with typical dialysate temperature (*Data set 1*).

In another subset of data, forty-eight HD patients were randomized either into an Exercise Group (EG=24) who received 7-month of IET or a Control Group (CG=24) where did not participated in any exercise training (*Data set 2*).

Participants from both subset of data were assessed for VL architecture using ultrasonography, functional capacity using a battery of functional tests (6 min walking test, 5 repetitions sit-to-stand, sit to stand 60sec, handgrip strength), and maximal aerobic power determined with a modified version of the Åstrand test. Parameters related to quality of life were determined using validated set of questionnaires.

Results: Cooling the dialysis temperature (CD) significantly, improved VL fascicle length compared with TD. In contrast, VL thickness significantly reduced showing a moderate effect size ($d>0.40$) in the TD group. (Data Set 1). VL fascicle angle and length did not change significantly between the two groups in the Data Set 2 ($P>0.05$). Muscle thickness decreased in CG ($p=0.02$, $p<0.05$) while it remained unchanged in the EG group (Data set 2). Physical performance and quality of life increased only in the EG compared to the CG (Data set 2).

Conclusions: The changes in dialysis temperature imposed an effect in muscle architecture of VL muscle. IET provides a time-effective stimulus for increasing the functional capacity in HD patients while muscle architectural changes may require longer and higher intensity exercise training stimulus or supplemented with resistance exercise to reveal clinically meaningful changes.

Keywords: intradialytic exercise, skeletal muscle architecture, end stage renal disease, muscle atrophy, functional test.

Introduction

Patients with end stage renal disease (ESRD) have compromised skeletal muscle mass, resulting in poor physical capacity, extreme fatigue which is associated with increased morbidity and mortality[73,76]. Hemodialysis (HD) is a life-saving replacement therapy for these patients, however, HD may result in a number of serious complications, including cardiovascular disease, protein malnutrition, insulin resistance, immune deficiency, anemia and muscle wasting[198]. Despite great advances in managing HD-related complications, muscle wasting is still an unresolved concern leading to frailty and disability. Muscle wasting is defined as unintentional body weight loss, which can be divided into loss of lean body mass and fat mass, and has been recognized as a common and major problem of chronic kidney disease (CKD) that affects patient mortality rates, daily activity, levels of fatigue, quality of life, immunity function, and numbers of days of hospitalization[199].

Cooling the dialysate temperature (cold dialysis; 35°C) contribute to the hemodynamic stability in patients during hemodialysis[29]. Specifically, cool dialysis (CD) observed beneficial effects in many aspect of the quality of life in ESRD patients[9]. However little know about the effect possible adaptations of the muscle during CD.

Intradialytic exercise training (IET) has been successfully used to ameliorate loss of muscle mass, restore muscle capillary bed and reduce muscle wasting[200]. Several studies have shown that IET causes changes in skeletal muscle histology, metabolism, endurance and bears optimal performance output[201]. Studies using muscle biopsies in ESRD patients undergoing IET, have shown reduced muscle protein catabolism increased mean muscle fibre cross sectional area and improving muscle force output and efficiency[90,202]. Still, the mechanisms underlying these improvements is not fully elucidated. Muscle architecture is defined as the internal arrangement of muscle fibers within a muscle and has been described as one of the primary determinants of muscle function[98]. Because the architecture of a muscle determines a large part of it's force-velocity properties, including outcome measures of muscle architecture may be of clinical importance. Such measures include physiological and anatomical cross-sectional areas, muscle thickness, the length of muscle fascicles (bundles of muscle fibers) as well as the angle of pennation of the fascicles[98]. Studies have showed that abnormal muscle architecture is more prominent in patients under HD than in patients with chronic renal failure not yet on dialysis[88]. Narici et al (2003) showed that the changes in muscle architecture play a significant role in the loss of muscle

function in elderly because they are likely to affect the length-tension as well as the force-velocity and power-velocity relations of this muscle on which common daily functions such as walking and stair negotiation depend[203]. Also, the existence of relationship between muscle architecture and performance and how training could alter the architecture of muscles have been shown in several previous studies of Blazevich[204,205]. Specifically, muscle architecture have been found to be associated with running, squat movement and jumping performance[206]. Nevertheless, data about how muscle architecture predicts muscle function in HD patients is limited. Schardong et al (2017), showed that there was a significant reduction in pennation angle of the right and left vastus lateralis (VL) muscle, after 8 weeks of neuromuscular electrical stimulation intervention[102].

However, despite a strong rationale for the implementation of IET and the improvement on muscle function and the major benefits of CD in general health of the ESRD patients, the effect of CD and IET on muscle architecture have not been investigated to date. Understanding the muscle's structural and functional relationship is of great practical importance, in order to provide significant information regarding underlying abnormalities, including skeletal muscle weakness, which is evident in patients undergoing chronic hemodialysis. As indicated above, we hypothesized that IET may be able to provide positive adaptations in skeletal muscle architecture in patients receiving hemodialysis leading to improved patient functional capacity and quality of life. The aim of the current study was to assess the effects of cold dialysis and 7-month of intradialytic exercise training (IET) on changes in vastus lateralis (VL) muscle architecture, functional capacity and quality of life in hemodialysis (HD) patients

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 individual dialysis centres. All patients gave their written informed consent prior to study participation.

Study Population

Data set 1: Fourteen haemodialysis patients participated in this study. Inclusion criteria: clinically stable condition, receiving regular hemodialysis treatment for at least 3 months, with adequate dialysis delivery Kt/V >1.1 and good compliance of dialysis treatment, serum albumin > 2.5 g/dL, hemoglobin ≥ 11g/dL and treatment with rHuEPO. Exclusion criteria: reason to be in a catabolic state, such as hyperthyroidism, active vasculitis, malignancies, pregnant HIV, opportunistic infections, myoskeletical contraindication to exercise, requirement for systemic anticoagulation, participant or participated in an investigational drug or medical device study within 30 days or five half-lives or inflammations, that required intravenous antibiotics within 3 months prior to enrollment, diabetics receiving insulin therapy, New York Heart Association grade IV heart failure, and mental incapacity to consent.

Data set 2: Forty-four haemodialysis patients fulfilled the inclusion criteria and participated in this study. The inclusion criteria for the study were: the patients were clinically stable, and they had received regular haemodialysis treatment for at least 3 months, with adequate dialysis delivery Kt/V >1.2 and good compliance of dialysis treatment, the serum albumin was > 3.0 g/dL, hemoglobin ≥ 11g/dL and treated with rHuEPO. The exclusion criteria for the study were: a reason to be in a catabolic state, such as hyperthyroidism, active vasculitis, malignancies, pregnant HIV, opportunistic infections, myoskeletical contraindication to exercise, requirement for systemic anticoagulation, participant or participated in an investigational drug or medical device study within 30 days or five half-lives or inflammations, that required intravenous antibiotics within 3 months prior to enrollment, diabetics receiving insulin therapy , New York Heart Association grade IV heart failure, and mental incapacity to consent.

Figure 1: Chat flow for the data set 1.

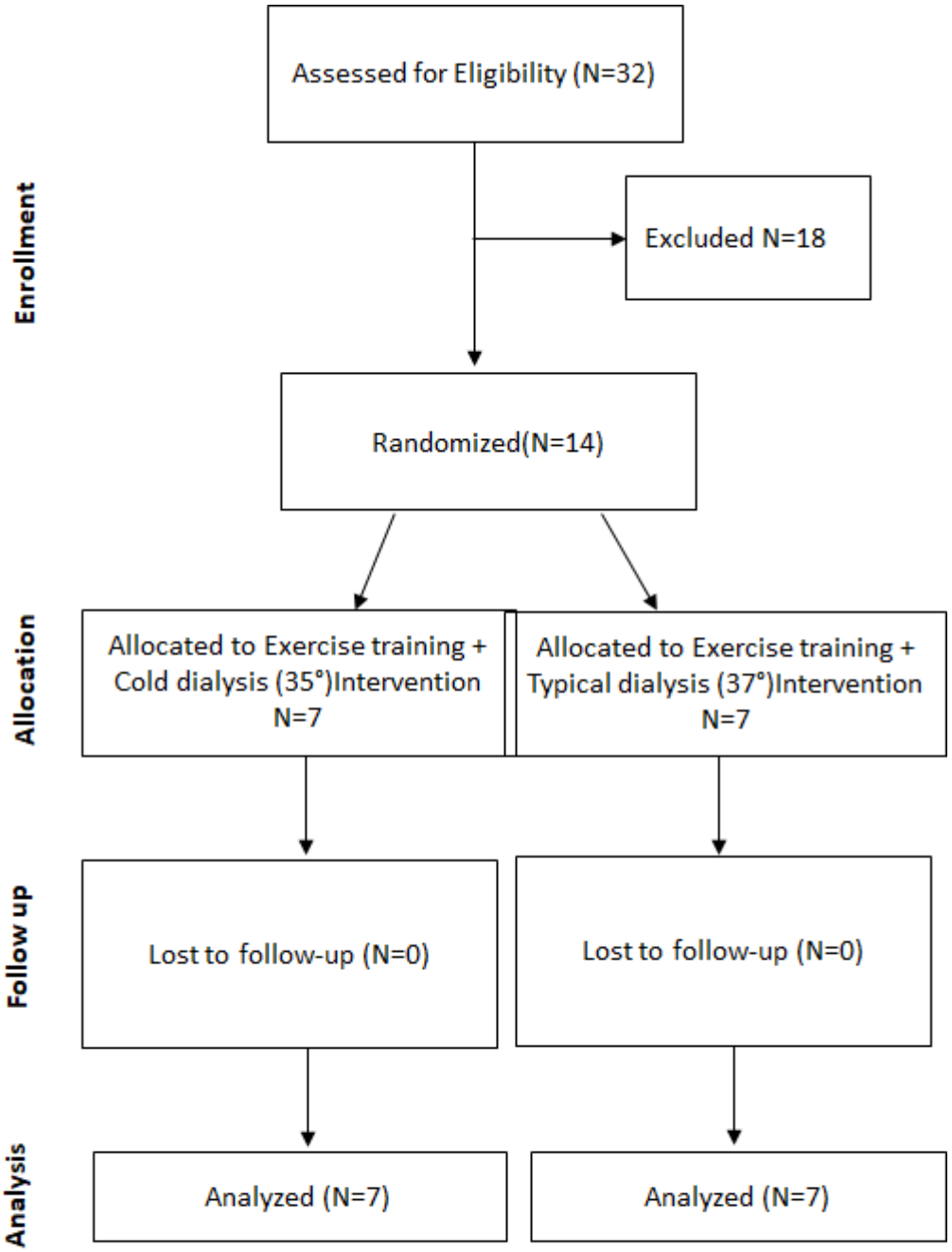
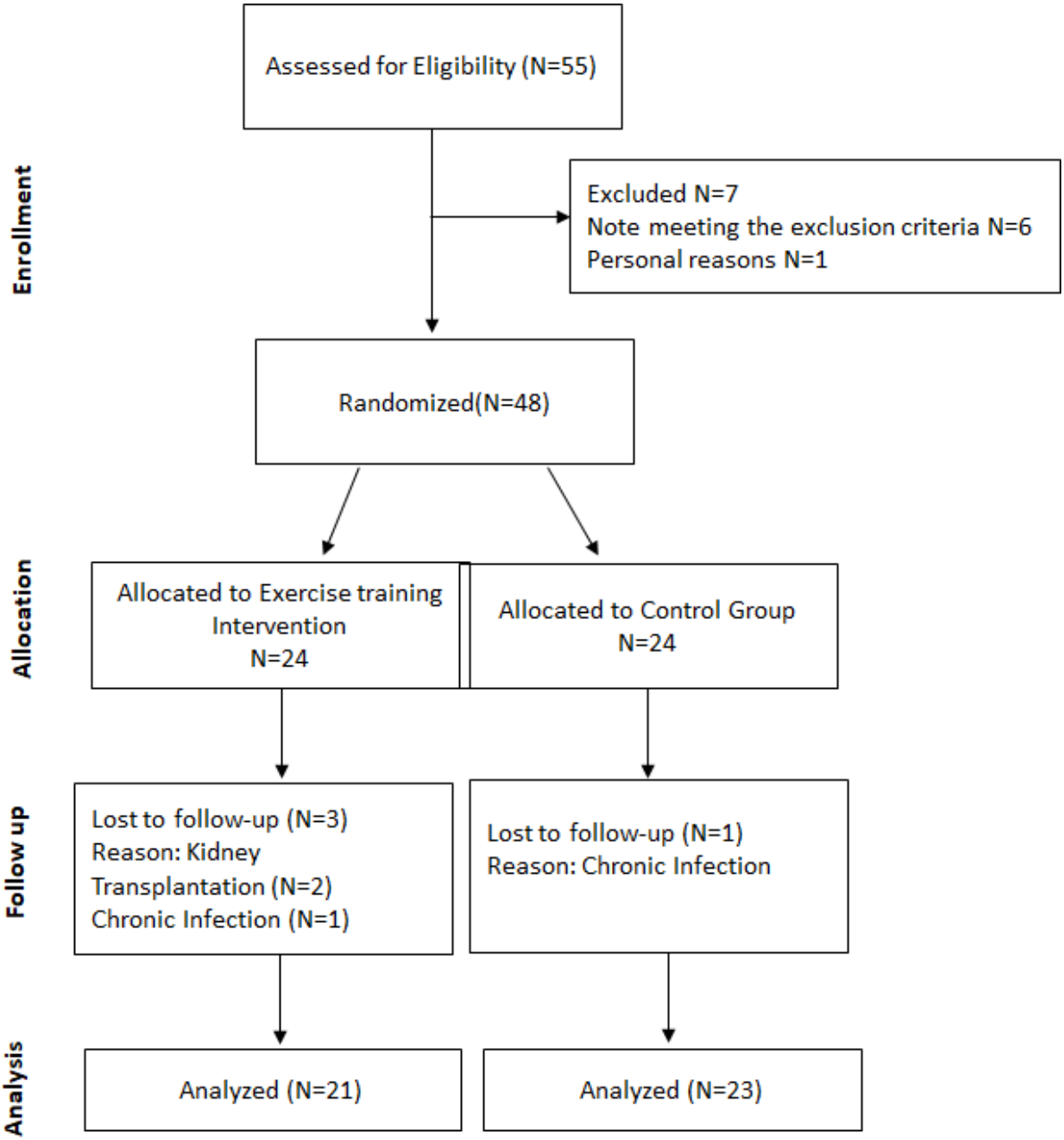


Figure 2: Chat flow for the data set 2.



Sample size

Data set 1: Sample size calculations were conducted based on thickness of vastus lateralise muscle and 6 minute walking test performance in the hemodialysis patients from a previous published article[102]. The resulting minimum required sample size was 11 for 2-sided type 1 and type 2 errors 5%. Sample size calculations were conducted using G*Power 3.0. The "Means: difference between two dependent means" method was used to calculate the power of the within effect. The current analysis seems to be underpowered.

Data set 2: Sample size calculations were conducted based on thickness of vastus lateralise muscle and 6 minute walking test performance in the hemodialysis patients from a previous published article[102]. The resulting minimum required sample size was 21 for 2-sided type 1 and type 2 errors 5%. Sample size calculations were conducted using G*Power 3.0. The "Means: difference between two dependent means" method was used to calculate the power of the within effect.

Study Design

Patients were recruited from the hemodialysis unit of General Hospital Trikala, Greece and the Eftychios Patsides General Clinic, Larisa, Greece. The study was performed from October 2016 to June 2018. Study measurements were performed at the metabolic ward of the General Hospital of Trikala, Greece and at the physiotherapy laboratory of the Eftychios Patsides General Clinic. Patients enrolled by a research using random generator for randomization. For the Data set 1 all participants received 7 months of supervised intradialytic aerobic exercise training. Patients were randomized by a randomization software and assigned in two groups: the Cold Dialysis (35°C) + Exercise Group (N=7) (CD+EX) and the Typical Dialysis (37°C) + Exercise Group (N=7) (TD+EX). All patients assessed for their body composition, functional capacity and muscle architecture. All measurements took place immediately after the cessation of the HD session and before and after the 7 months experimental intervention (Data set 1).

For the Data set 2, patients were randomly assigned in two groups: the Exercise Group (N=21) which received 7 months of intradialytic exercise training and the Control Group (N=23) which did not receive intradialytic exercise during dialysis session. All patients were assessed for their body weight and height, body composition, physical activity, functional capacity. Questionnaires were used to evaluate the quality of their life, symptoms of restless legs syndrome (RLS) and fatigue severity. Also, the architecture of

vastus lateralis muscle was evaluated with ultrasonography. All measurements were performed before (trial 1) and after (trial 2) the experimental intervention.

Hemodialysis Procedure

The patients underwent hemodialysis therapy (Fresenius 4008B, Oberursel, Germany) three times per week with low flux, hollow fiber dialyzers and bicarbonate buffer. The hemodialysis sessions had a mean duration of approximately 4 hours. Erythropoietin therapy (EPO) was given after the completion of hemodialysis session (HD) in order to normalize hemoglobin levels within 11–12 (g/dL) as well as monthly intravenous iron infusions (Ferinject ©) for stabilizing Iron and Ferritin levels.

Body Composition Assessment

The patient's whole body, regional fat and lean body mass were measured by Body Composition Monitor (BCM - Fresenius Medical Care, Deutschland GmbH) which has been specifically designed for patients with kidney failure. Body composition was assessed in a separate dialysis day before start the experimental intervention and in a separate dialysis day after the completion of the experimental intervention. All measurements were performed immediately after dialysis session, where the patients were in a supine position, for the proper recording of the measurement, was allowed only water intake from the patients during dialysis.

Physical Activity Assessment

Physical activity was measured by using pedometer (Digi-Walker, SW-200 pedometer), which was given to each participant. Participants were instructed to attach the pedometer at the waistline each morning and to wear the pedometer throughout the day while doing usual activities, except during bathing. They were asked to remove the pedometer before going to bed and to record the day's step count each night before resetting the device to zero for the next day. Physical activity recorder, was held one week (7 days) before the experimental intervention started and one week (7 days) after the completion of the experimental intervention.

Functional & Maximum Power Capacity Assessment

Muscle functional capacity was assessed using the following tests: 1) time to perform five sit-to-stand cycles (STS-5), 2) number of sit to stand cycles achieved in 60 second (STS-

60s), 3) time to walk a distance of 6m at fast pace (FWT6m), 4) six minute walking distance (6MWT) were patients covered the longer possible distance while walking for six minutes on a level surface (hospital corridor) without pre-warming, 5) right hand grip test hang their hand by their side, when are ready the patients squeezes the dynamometer with maximum isometric effort, which is maintained for about 5 seconds. At least one of the researchers was present during the testing of functional capacity and encouraged patients to perform their best. All functional capacity tests were performed, separate dialysis day before start the experimental intervention (trial 1) and in a separate dialysis day after the completion of the experimental intervention (trial 2) both groups. The ICC for functional capacity test has been described before by Overend et al (2010), Ortega -Pe´rez de Villar et al (2018) and Segura-Ort et al (2011). The patients' maximum power capacity was determined by a modified version of the Åstrand Bicycle Ergometer test protocol at bedside on a previous dialysis session during hemodialysis. The maximum power capacity test performed, one week before the start of experimental intervention (trial 1) and one week after the the completion of the experimental intervention (trial 2) in both groups (Data set 2).

Questionnaires

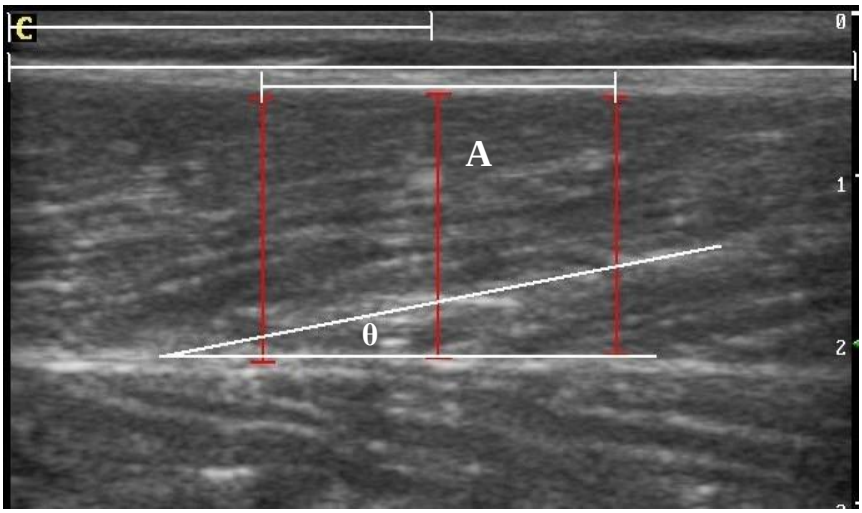
The questionnaires were completed with the interview method by experienced personnel. Quality of life was assessed by using the SF36 QoL questionnaire adjusted and validated in dialysis patients. Fatigue Severity was assessed by using Fatigue Severity Scale. All questionnaires were completed separate dialysis day before start the experimental intervention (trial 1) and in a separate dialysis day after the completion of the experimental intervention (trial 2) in both groups. Questionnaires were completed immediately after dialysis session, in the same order as described above.

Muscle Architecture

All ultrasound images obtained 3 days before the initiation (trial 1) and 3 days after the completion of the experimental intervention (trial 2) in both groups. The ultrasonography performed, with the patient's in the supine position after resting for 15 min and having been advised not to perform any vigorous physical activity in the 72 h prior to the examination. B-mode ultrasound images were obtained from the right vastus lateralis using a 40mm linear probe (4.8 MHz, CHISON Digital Color Doppler Ultrasound System, Model Q8, China). Patients laid supine with their knees fully extended and their muscles

relaxed. Sonographs were taken at the middle distance between the central palpable point of the greater trochanter to the lateral condyle of the femur. A water-soluble gel was applied to the transducer to aid acoustic coupling and reduce the needed pressure from the probe against the muscle. The transducer was placed longitudinal at femur, oriented in parallel to the muscle fascicles and perpendicular to the skin. Due to individual differences, the transducer was sometimes aligned slightly diagonally to the longitudinal line of the muscle. Images were analyzed for muscle thickness, fascicle angle and fascicle length with image analysis software (Motic Images Plus,2.0, Hong Kong). Muscle thickness was defined as the mean of the distance between the superficial and deep aponeurosis measured at the ends of each 40mm wide sonography, fascicle angle as the angle of insertion of muscle fascicles into the deep aponeurosis and fascicle length as the fascicular path between the insertion of the fascicle into the upper and deeper aponeurosis.

Image 1: Ultrasound imaging of the Vastus Lateralis (VL) muscle, that showing A) the thickness (cm) of the VL muscle, B) the pennation angle (θ°) of the VL muscle. Based on the VL thickness and the VL pennation angle in the same ultrasound image, we estimated the VL fascicle length (cm) of the VL muscle[1].



Intradialytic Exercise Protocol

All exercise groups (Data set 1 & 2) performed cycling for 60 minutes at a supine position. During the sessions, the patients were asked to pedal at 45 rpm for the first 10 minutes and then at 60 rpm on a bedside cycle ergometer (Model 881 Monark Rehab Trainer, Monark Exercise AB, Varberg, Sweden). Patients cycled at approximately 60% of their pre-assessed maximum power capacity. The exercise regime started 1st and 2nd hour of

the hemodialysis session. Exercise was well tolerated by all patients, and no adverse reactions were reported.

Statistical Analysis

A Multivariate Analysis of Variance (MANOVA) followed by post-hoc paired-samples t tests were used to assess the effects of time (pre / post) and protocol (CD+EX vs TD+EX, and EG vs CG). The MANOVA results demonstrated no statistically significant main or interaction effects. To further strengthen the analysis, Cohen's d effect sizes (0.2-0.5: small effect; 0.5-0.8: moderate effect; >0.80: large effect) were also used to identify paired differences between protocols and times. Data are expressed as mean±SD. Statistical significance was accepted at $p<0.05$. All analyses were carried out using the Statistical Package SPSS 21.

Results from Data set 1

Patient's characteristics are presented in Table 1.

Table 1: Patient's characteristics from the (Data Set 1)
(the same as in Table 1 in Study 3)

Variables	CD+EX	TD+EX
N	7	7
Male/Female	7/0	3/4
Age (yr)	63.57±9.93	52.71±16.84
Dry Weight (kg)	75.86±7.45	63.65±13.13
Height (cm)	172.8±7.40	167.1±5.76
BMI (kg/m^2)	25.54±2.48	22.80±4.17
WHR	0.97	1.02
TBW	38.30	31.31
ECW	16.77	14.07
ICW	21.51	17.22
E/I	0.80	0.82
LTM (kg)	58.78	55.78
FAT(kg)	24.48	30.65
Years in Hemodialysis	8.14±2.90	8.71±3.10
Hct	35.58±3.02	35.94±2.91
Hb (g/dl)	11.14±1.14	11.56±0.71
Albumin (g/dl)	4.17±0.15	4.28±0.36

Note: All data are mean ± SD. Abbreviations: BMI, Body mass index; WHR, waist hip-ratio; TBW, total body water; ECW, extracellular water, ICW, intracellular water; E/I, extracellular-intracellular water ratio; LTM, lean total mass; Hct, Hematocrit; Hb, Hemoglobin.

Table 2. Changes in ultrasonography and physical activity levels between CD+EX and TD+EX groups (Data Set 1).

Variables	CD+EX			TD+EX			Between Groups	
Muscle Architecture	**Pre**	**Post**	**P value (effect size)**	**Pre**	**Post**	**P value (effect size)**	**P value Pre (effect size)**	**P value Post (effect size)**
VL Thickness (cm)	1.89±0.37	1.79±0.46	0.48$^{(0.22)}$	2.04±0.55	1.79±0.59	**0.06**$^{(0.41)}$	0.70$^{(0.29)}$	0.99$^{(0.00)}$
VL fascicle angle (°)	11.71±2.09	12.19±2.13	0.44$^{(0.21)}$	13.84±3.05	14.00±3.27	0.77$^{(0.05)}$	0.56$^{(0.75)}$	0.27$^{(0.60)}$
VL fascicle length (cm)	4.18±3.42	7.17±3.47	**0.05**$^{(0.80)}$	8.62±1.76	7.37±1.61	0.35$^{(0.69)}$	0.40$^{(1.56)}$	0.89$^{(0.07)}$
Physical Activity (steps/day)	5589±1204	6420±7619	**0.06**$^{(0.15)}$	4926±1718	5665±2130	0.07$^{(0.38)}$	0.48$^{(0.44)}$	0.76$^{(0.13)}$

Note: VL: Vastus Lateralis; Significance level P<0.05.

Cooling the dialysis temperature (CD) significantly, improved VL fascicle length compared with TD (Table 2). In contrast, VL thickness significantly reduced showing a moderate effect size (d>0.40) in the TD group.

Results from Data set 2

Patients' characteristics are presented in Table 3.

Table 3. Characteristics of the patients presented as pooled data as well as for each group (Exercise Group vs. Control Group) (Data set 2)

Variable	All Patients	Exercise Group	Control Group
N	44	21	23
Gender (Female/Male)	18/26	5/16	13/10
Age (yr)	67.20±13.02	66.04±15.35	68.26±11.07
BMI (kg/m^2)	24.40±3.21	24.49±3.84	24.35±2.58
Dry Weight (kg)	69.10±9.99	69.86±10.24	68.41±9.94
Height (cm)	168.20±7.72	169.14±7.17	167.39±8.26
Years in Hemodialysis	6.3±4.9	7.29±4.0	5.39±5.55

Note: BMI: body mass index.

No statistical significant differences were found between the two goups.

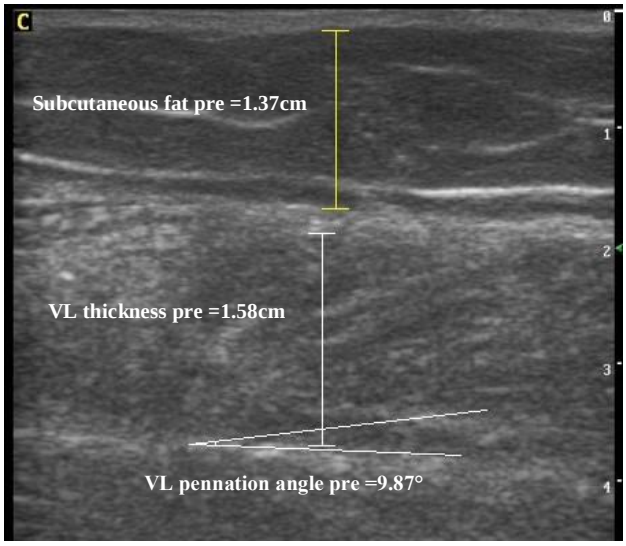
In the Data set 2, intradialytic exercise training (IET) did not induce any significant changes in VL thickness, fascicle angle or fascicle length (Table 4). In contrast, VL thickness was significantly decreased in the control group (CG) after the lack of intervention (p=0.02). There was a significant difference at the end of the intervention period between groups (post values) in VL fascicle angle (p=0.04, Table 2).

Table 4. Changes in ultrasonography indices after 7 months of intradialytic exercise training (Data set 2).

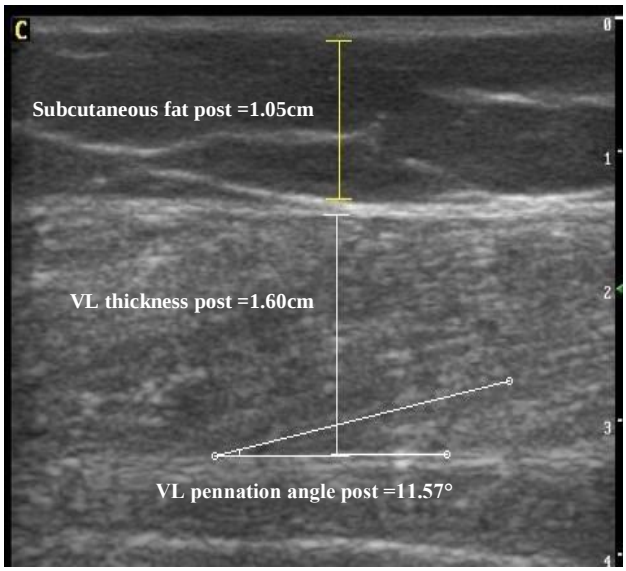
Variables	Exercise group (N=21)			Control Group (N=23)			Between Groups
	Pre	Post	P value (Effect size)	Pre	Post	P value (Effect size)	P value (Effect size)
VL Thickness (cm)	1.92±0.42	1.81±0.43	0.15 (0.25)	1.84±0.53	1.67±0.45	**0.02** (0.34)	0.28 (0.31)
VL fascicle angle (°)	12.25±2.81	12.51±2.91	0.49 (0.09)	11.15±2.94	10.79±2.61	0.37 (0.13)	**0.04** (0.61)
VL fascicle length (cm)	6.37±3.67	6.78±2.81	0.70 (0.12)	6.00±3.38	5.97±2.82	0.95 (0.01)	0.34 (0.28)

Note: VL: Vastus Lateralis; (Cohen's d), d=0.20-0.50 small, d=0.50-0.80 moderate, d>0.80 large effect size; Significance level P<0.05.

Image 2: Indicative example of changes in vastus lateralis (VL) muscle thickness and pennation in a hemodialysis patient. (A) Pre and (B) Post participating in the 7month of intradialytic exercise training. Changes in muscle architecture, as well as in fat thickness are indicated.



(A) Pre
7-months of Intradialytic Exercise Training (IET)



(B) Post
7-months of Intradialytic Exercise Training (IET)

Performance in STS-60sec was increased after IET (10.23±1.58%) as well as the 6min walking distance (17.19±14.62%, Table 5). Hand grip strength was also increased after IET (5.13±28.28%) as well as the maximal aerobic power during the modified version of the Åstrand Bicycle Ergometer test (26.35±1.22%, Table 5). No significant differences in functional capacity were observed in the CG (Table 5). There was no statistically

significant correlation between the changes in muscle architecture and performance for either of the two groups.

Table 5. Functional capacity test and body composition data before and after 7 months of intradialytic exercise training (Data set 2).

Variables	Exercise Group (N=21)				Control Group (N=23)			
	Pre	Post	P value	Effect size	Post	Post	P value	Effect size
Functional capacity test								
STS-5 (min)	11.71±7.13	11.30±7.17	0.40	0.05	11.63±3.47	11.65±3.44	0.92	0.01
STS-60 (rep)	23.45±6.23	25.85±6.33	**0.00**	0.37	21.22±3.88	21.70±4.33	0.35	0.11
6m Fast Walk (sec)	3.78±1.09	3.75±1.07	0.87	0.03	4.00±0.93	4.01±0.97	0.84	0.01
6min Walk Test (m)	404.3±99.5	468.1±87.2	**0.00**	0.67	381.9±76.0	383.0±77.1	0.72	0.01
Hand Grip (kg)	29.14±7.03	30.64±9.02	**0.02**	0.19	23.08±6.28	23.98±7.25	0.06	0.13
Max test (watt)	39.76±20.15	50.24±20.40	**0.00**	0.51	32.65±12.76	33.24±15.20	0.82	0.04
Phy. Activity (step)	5913±4811	6317±4629	0.08	0.08	3203±2195	3037±2188	0.57	0.07
Body composition								
LTM (kg)	38.30±9.60	38.24±8.95	0.91	0.01	24.07±6.1	24.24±6.53	0.25	0.03
% LTM	53.43±12.09	53.20±11.46	0.72	0.02	34.63±6.26	34.80±6.63	0.41	0.03
Fat (kg)	25.60±10.99	25.64±10.74	0.92	0.00	24.08±4.87	23.80±4.58	0.56	0.06
% Fat	32.43±10.72	32.54±10.54	0.81	0.01	34.20±3.64	34.04±4.72	0.74	0.04

Note: STS-5: five sit to stand cycles; STS-60: sit to stand cycles in 60 second; LTM: lean total mass; Max test: maximal power during the modified Astrand test. Cohen's d, d=0.20-0.50 small, d=0.50-0.80 moderate, d>0.80 large effect size; Significance level P<0.05.

In Data set 2, after 7 months of IET, significant improvements ($p<0.05$) were found in several aspects of the quality of life such as general health, physical health and mental health (Table 6). An important factor is the vitality subscale showing significant evidence of improvement after the exercise intervention while in contrast, general health and fatigue were significantly worsened after 7 months abstention from IET (Table 6)

Table 6. Quality of life and fatigue severity parameters before and after 7 months of intradialytic exercise training (Data set 2).

Variables	Exercise Group (N=21)				Control Group (N=23)			
	Pre	Post	P value	Effect size	Pre	Post	P value	Effect size
SF-36 Quality of life								
Physical Function	87.5±17.8	88.7±16.6	0.13	0.00	92.3±8.2	92.8±6.9	0.60	0.07
Role Function	90.5±12.9	91.0±13.5	0.69	0.04	96.5±4.7	96.8±4.4	0.74	0.06
Body Pain	94.0±9.9	95.0±11.0	0.60	0.09	95.2±8.4	95.7±7.6	0.74	0.06
General Health	80.9±16.0	87.3±12.1	**0.00**	0.44	90.8±11.4	89.3±12.7	**0.05**	0.13
Vitality	87.2±13.7	94.0±7.5	**0.03**	0.60	94.2±7.8	93.9±7.1	0.81	0.03
Role Emotional	91.1±13.5	93.4±12.2	0.29	0.17	89.6±13.7	90.5±11.3	0.66	0.07
Mental Health	75.7±6.3	77.1±5.0	0.20	0.24	79.0±6.5	79.3±7.6	0.74	0.04
Physical Health	87.9±10.7	91.2±9.3	**0.01**	0.32	93.8±5.7	93.7±5.1	0.86	0.02
Mental Health	87.0±7.5	90.3±5.7	**0.00**	0.48	90.5±6.3	90.4±5.8	0.83	0.02
Total	88.4±8.3	90.7±7.3	**0.00**	0.29	92.3±5.1	92.3±4.8	1.00	0.00
Fatigue Severity Scale								
FSS	3.38±1.07	3.36±1.14	0.80	0.02	3.63±0.96	3.86±1.13	**0.00**	0.22

Note: Cohen's d, d=0.20-0.50 small, d=0.50-0.80 moderate, d>0.80 large effect size; Significance level P<0.05.

Discussion

The present study, sought to assess changes in vastus lateralis (VL) muscle architecture in dialysis patients, after seven months cold dialysis and intradialytic exercise training (IET) or lack of systematic activity. The main findings of the current study showed that 7 months of cold dialysis in conjunction with IET showed evidence of improvements in fascicle length of VL compared to TD group (Data Set 1). In addition aerobic IET was enough to improve the functional capacity and maintained quadriceps muscle thickness of the EG group (Data Set 2) leading to a substantial improvement in many aspects of quality of the life and overall health. The current results suggest that aerobic IET provides a time-effective stimulus for increasing the functional capacity of ESRD patients while it provides an adequate stimulus for halting muscle cachexia and deconditioning[207].

This is the first study that attempts to assess the muscle architecture of VL under different dialysate temperatures. Our results showed that cooling dialysate temperature could induce favorable changes in morphological characteristics in VL muscle architecture.

To the best of our knowledge, this is the first study to show changes related to CD and muscle architecture. There is no clear explanation for the current evidence however, a potential hypothetical explanation could be lie within aspects related to dialysis adequacy. More specifically better dialysis adequacy is related to better nutritional status and therefore higher levels of muscle mass. It's known the cooling of the dialysate temperature increases vascular resistance making more blood flow available to rich active tissues such as skeletal muscles. In this case, the body gets access to "hidden" compartments within the skeletal muscles. The increased blood flow that follows exercise activity mobilizes the intramuscular urea and creatinine and transfer them into the systemic circulation and from there and through the hemodialysis filter outside the patients' body. It might be also suggested that the vasoconstriction of the nonworking muscles in conjunction to the CD might induce a stronger stimulus, superior or additive to the vasodilatative one, leading to a reduction of the perfused volume and thus a better/faster solute removal as a consequence[201]. Therefore, CD and exercise could improve dialysis adequacy affecting nutritional status leading to better quality of muscle tissue. It important to note that of the three organs (muscle, skin, and bone) that contain most of the total body water and hence urea and creatinine, muscle is by far the most clinically important. Studies showed that one of the major chronic effect of CD is the reduction of urea rate[154]. However, these hypothesis remained approved and no matter how reasonable it sounds, more evidence are needed to further validate such explanation.

Even though, the impact of IET on patients health is very well documented, the effect on skeletal muscle architecture is not well studied in this patients population. Studies showed that aerobic IET improves muscle function, in patients with ESRD[94]. Specifically, it has been reported that the cross-sectional area of type I and II muscles fibers obtained from vastus lateralis muscle, increased after 6 months of intervention[94]. In addition, ultrastructural analysis revealed positive adaptations in muscle capillaries and mitochondria post intervention[208]. By contrast, Moore et al (1993) observed no muscle hypertrophy secondary to 6 months of intradialytic aerobic training, which is not unexpected given that aerobic training, is not the preferred exercise modality for eliciting myogenic adaptation[127]. Similar results demonstrated by the study of MacDonald et al (2005) where after 12 weeks of intradialytic cycle exercise failed to reverse the muscle atrophy which characterize this population[209].

Failure of the intradialytic aerobic exercise training (Data Set 2) to provide changes in vastus lateralis architectural structure may be due to the insufficient exercise intensity to provide an anabolic response in promoting muscle hypertrophy in these patients. Previous studies which suggested that the aerobic exercise may have anabolic effects in uremic patients, used longer exercise duration (e.g. 90-min), on non-dialysis days[94].

In the data set 2 study, the IET induced significant improvements in patient's performance. Despite the non-statistical significant changes observed in the architectural structure of the muscle, the functional capacity of the patients undergoing exercise improved significantly compared to current practice (no exercise training – CON). A possible explanation for such improvement might be linked with central, intermediary and peripheral cardiorespiratory system adaptations to exercise training. Storer et al (2005) reported that the observed increase in muscular strength in response to aerobic exercise in ESRD patients was accompanied by changes in skeletal muscle growth factors, including a decrease in myostatin mRNA and an increase in IGF-1 receptors, suggesting severe deconditioning of these patients[121]. Aerobic exercise training may be an adequate stimulus for muscle hypertrophy in such patients. In addition, the significant reduction of the muscle thickness after 7 months of abstaining from IET seems to have also affected the functional capacity of the patients. Previous studies that assessing muscle architecture in elderly showed the significant link between muscle thickness and functional performance in this population[203].

Several trials of exercise training in hemodialysis patients have evaluated SF36 scores as health-related quality of life outcome measures. Improved perceptions of physical

functioning have been observed secondary to 3–5 months of aerobic exercise training[14]. Painter et al (2000) reported improvements in role physical, bodily pain, general health, vitality and the physical component scale, especially in patients with low baseline perceptions of physical functioning[173]. Overall, intradialytic exercise training can induce positive effects in health and clinical condition in this cohort, which may be associated with enhanced quality and quantity of life. To enable design of the most efficient training protocols, require confirmation by further prospective studies to determine the relative importance of factors such as mode, intensity and duration of the anabolic response in ESRD.

Conclusion

This is the first study to assess muscle architectural changes in response to cold dialysis and chronic intradialytic exercise training in patients with ESRD. Cold dialysis in conjunction with IET showed evidence of improvements in fascicle length of VL compared to TD group reducing thus the catabolic effect of the uremia and the hemodialysis procedure *per se*. Intradialytic exercise training increases muscle strength and impose a protective beneficial effect against muscle atrophy of the lower limbs in patients with ESRD. It is evident, that dialysis at 35ºC and intradialytic exercise training should be the initial strategy of rehabilitation and treatment of muscle atrophy for this patients' population, improving low tolerance to exercise which often rendering conventional training unfeasible. In addition, ultrasonography can assess muscle architecture and has considerable relevance for physical exercise and rehabilitation practices. Ultrasound is affordable, portable, and more accessible than magnetic resonance imaging and computerized tomography and could easily be implemented into a renal rehabilitation setting for monitoring of muscle atrophy in patients with ESRD.

General Discussion

The present PhD thesis sought to assess the acute and chronic effects of cold dialysis (CD) and intradialytic exercise training (IET) in aspects related to quality of life and health in ESRD patients receiving hemodialysis therapy. The experimental design of the studies, gave us the opportunity to observe for the first time changes during the separate and combined effects of CD and IET in the parameters relate to thermoregulatory responses, insulin sensitivity, Vastus Lateralis muscle architecture and general aspects of quality of life in HD patients.

Our results show that the acute thermoregulatory responses during different dialysis temperatures, separated or combined with IET provided a different thermal load and heat stress in HD patients. Specifically the dialysate temperature to 37°C separated or combined with IET associated with increased body heat storage leading to hyperthermia. It well know that dialysate temperatures at 37°C is associated with an increase in core body temperature, shown to interfere with the appropriate hemodynamic response to body fluid removal, thus favoring the onset of hypotensive episodes especially in frail patients[35,41]. In addition, our results show that reducing the dialysate temperature to 35°C (cold dialysis), separated or combined with IET can prevent the rise of body heat storage and core temperature even during the period that IET took place (heat stress is increased during exercise). Cooling of dialysate fluid temperature below 36.5°C has been proposed as a factor contributing to hemodynamic stability in patients during HD[210]. Maggiore et al (1981) proposed cool dialysis to prevent intradialytic hypotension by increasing peripheral vascular resistance, improving cardiac output, and altering the levels of vasoactive peptides[29].

Other important results for our study show that a single session of CD and IET may provide an “acute” time-effective stimulus for improvement of OGTT, leading to a better hemodynamic support to HD patients especially during the CD, however none of the results showed statistically significant direction. In contrary, chronic effect of CD and IET showed that the reduction of dialysate temperature by 2°C induced favorable changes in aspects related to insulin sensitivity and glucose disposal. However, the exact underline mechanism of the improvement in the glucose disposal and insulin resistance of uremic patients after the initiation of the hemodialysis treatment it not clear. Limited information exist in the literature about the effects of CD in glucose metabolism and IR. Recently evidences suggest that “cold” in general (not in dialysis) activates brown adipose tissue[68], and therefore, the benefits of CD may be related to this effect[10]. In addition, studies have shown

that CD contributes to the secretion of endorphins which promote better consumption of glucose from the peripheral tissues[46].

Also the results of the CD, they once again showed its positive effects on hemodynamic changes, reducing thus possible hypotension symptoms. It has been proposed that during typical dialysis (37°C), the combination of low blood volume and loss of peripheral vascular resistance causes hypotension[211]. Loss of vascular resistance is multi factorial in cause, but uremic autonomic insufficiency, vasodilation from thermal amplification, and paradoxical withdrawal of sympathetic activity are believed to have the most important roles[7,8]. The improvement in blood pressure by using CD may be due to increased total peripheral resistance and increased venous tone[34]. Cooling dialysate temperature also improves left ventricular contractility independently of pre and after load[9].

It‘s important to denote that our results show that IET improved overall exercise capacity and indices of quality of life, irrespective dialysate temperature. CD and IET enhances health benefits improving overall patients' quality of life. Recent studies showed that IET, increase exercise tolerance which seems to be correlated with symptomatic improvements and enhancements in health-related quality of-life measurements[173,212] Improvements in measures of fatigue, activities of daily living, symptoms of peripheral neuropathy and myopathy, breathlessness, depression, and anxiety, as well as general wellbeing after exercise training are also reported[114,173]. Also, exercise training is found to improve skeletal muscle endurance and strength and, thus, peak exercise performance in HD patients[174]. Biopsy studies have demonstrated an increase in both Type I and Type II muscle fiber cross sectional areas after both endurance and strengthening training in chronic uremic patients[94]. In addition, regeneration of degenerated fibers, increase capillary density as well as the structure and number of mitochondria of the muscle[212]. However, the inability of our study to show statistically significant changes in muscle architecture of VL may be due to the fact that require higher exercise training loading or supplementary resistance exercise to reveal clinically meaningful changes. These results concur with the results of Moore et al. (1993) who have not found any significant morphological change in skeletal muscle after 12 weeks of cycling[127] and in contrast to Sakkas et al, (2003) who found 43% improvements in muscle cross sectional area after 6 months of aerobic training[208]. Nonetheless, it is very important the fact that IET provides a time-effective stimulus to maintain the architectural structure of the VL muscle and increasing the functional capacity in HD patients. In contrast to that, cold dialysis in conjunction with IET showed significant evidence of improvements in fascicle length of VL compared to TD

group enhancing further our hypothesis that CD could enhance the impact of IET on ESRD patients.

From the current thesis, it is evident that reducing the dialysate temperature from 37ºC to 35ºC we managed to reduce various risk factors for cardiovascular diseases and to improve the effectiveness of the exercise stimulus in patients with ESRD receiving hemodialysis therapy.

General Conclusions& Future Perspective

The present study it's the first clinical trial that try to assess the "acute" and "chronic" effects of the separated and combined adaptations of intradialytic exercise training with cooling dialysate fluid temperature.

From the current thesis, it is evident that reducing the dialysate temperature from 37ºC to 35ºC we managed to reduce various risk factors for cardiovascular diseases and to improve the effectiveness of the exercise stimulus in patients with ESRD receiving hemodialysis therapy. Further research may lead to patient-specific dialysate temperature profiling which will not only prevent the intradialytic hypotension but the excessive rise of heat storage and maximize the beneficial effects of the IET. In addition, large randomized trial are need to understand the differential benefit from CD as well as the underling physiological mechanism of the combined effects of CD with IET.

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Appendix

Appendix 1: Bioethics Approval

ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ
ΤΜΗΜΑ ΕΠΙΣΤΗΜΗΣ ΦΥΣΙΚΗΣ ΑΓΩΓΗΣ ΚΑΙ ΑΘΛΗΤΙΣΜΟΥ

Εσωτερική Επιτροπή Δεοντολογίας

Τρίκαλα; 5/11/2014
Αριθμ. Πρωτ.:921

Αίτηση Εξέτασης της πρότασης για διεξαγωγή Έρευνας με τίτλο: The effect of exercise rehabiliation regimes in combination with changes in dialysis procedures in aspects related to quality of life and health in end stage renal disease patients *(Η επίδραση της θεραπευτικής άσκησης σε συνδιασμό με αλλαγές στην θεραπεία της αιμοκάθαρσης στους δείκτες ποιότητας ζωής και υγείας σε ασθενείς με τελικού σταδίου νεφρική νόσο)*.

Επιστημονικώς υπεύθυνος-η / επιβλέπων-ουσα: Σακκάς Γεώργιος
Ιδιότητα: Λεκτορας
Ίδρυμα: Πανεπιστήμιο Θεσσαλίας
Τμήμα: Τμήμα Επιστήμης Φυσικής Αγωγής και Αθλητισμού

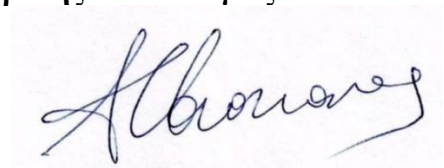
Κύριος ερευνητής-τρια / φοιτητής-τρια:
Κρασέ Αργυρώ **Πρόγραμμα Σπουδών:**
ΠΜΣ «Άσκηση και Υγεία» **Ίδρυμα:**
Πανεπιστήμιο Θεσσαλίας

Τμήμα: Τμήμα Επιστήμης Φυσικής
Αγωγής και Αθλητισμού
Η προτεινόμενη έρευνα θα είναι:
Ερευνητικό πρόγραμμα **X** Μεταπτυχιακή διατριβή ☐ Διπλωματική εργασία ☐ Ανεξάρτητη έρευνα ☐

Τηλ. επικοινωνίας: 6978509102
Email επικοινωνίας: gsakkas@med.uth.gr

Η Εσωτερική Επιτροπή Δεοντολογίας του Τ.Ε.Φ.Α.Α., Πανεπιστημίου Θεσσαλίας μετά την υπ. Αριθμ. 3-4/5-11-2014 συνεδρίασή της εγκρίνει τη διεξαγωγή της προτεινόμενης έρευνας.

Ο Πρόεδρος της Εσωτερικής
Επιτροπής Δεοντολογίας – ΤΕΦΑΑ



Τσιόκανος Αθανάσιος
Αναπληρωτής Καθηγητής

Appendix 2: Consent Form

ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ
ΤΜΗΜΑ ΕΠΙΣΤΗΜΗΣ ΦΥΣΙΚΗΣ ΑΓΩΓΗΣ ΚΑΙ ΑΘΛΗΤΙΣΜΟΥ

Έντυπο συναίνεσης δοκιμαζόμενου σε ερευνητική εργασία

Τίτλος Ερευνητικής Εργασίας: Επίδραση της οξείας άσκησης και της μείωσης της θερμοκρασίας του διαλύματος αιμοκάθαρσης στη διέγερση του φαιού λιπώδη ιστού και στην αντίσταση της ινσουλίνης σε άτομα με χρόνια νεφρική ανεπάρκεια.

Επιστημονικός Υπεύθυνος: Σακκάς Γεώργιος, Επίκουρος Καθηγητής, ΤΕΦΑΑ, ΠΘ, email:gsakkas@med.uth.gr, τηλ.: 2431-500901

Ερευνητές: Αργυρώ Κρασέ (email: argyrokrase@hotmail.com, τηλ. 6934734874) και Αικατερίνη Πόπτση (apoptsi@uth.gr)

1. **Σκοπός της ερευνητικής εργασίας**

Σκοπός της μελέτης είναι η αξιολόγηση της επίδρασης της μίας συνεδρίας άσκησης σε συνδυασμό με τη μείωση της θερμοκρασίας του διαλύματος αιμοκάθαρσης (1°C κάτω από την κλασική θερμοκρασία), στη διέγερση του μεταβολισμού και στην αντίσταση στην ινσουλίνη σε άτομα με χρόνια νεφρική ανεπάρκεια τελικού σταδίου.

2. **Διαδικασία**

Για τις ανάγκες της μελέτης θα αξιολογηθείτε 4 φορές στο νοσοκομειακό χώρο την ημέρα της προκαθορισμένης αιμοκάθαρσης. Την πρώτη ημέρα της αξιολόγησης (πρώτη εβδομάδα) θα πραγματοποιηθεί η κλασική προκαθορισμένη αιμοκάθαρση. Τη δεύτερη ημέρα αξιολόγησης (δεύτερη εβδομάδα) η θερμοκρασία διάλυσης της αιμοκάθαρσης θα είναι 1°C κάτω από την κλασική θερμοκρασία. Την τρίτη ημέρα αξιολόγησης, (τρίτη εβδομάδα) κατά τη διάρκεια της αιμοκάθαρσης θα πραγματοποιηθεί πρόγραμμα άσκησης ενώ την τέταρτη ημέρα αξιολόγησης (τέταρτη εβδομάδα) κατά την διάρκεια της αιμοκάθαρσης θα πραγματοποιηθεί πάλι πρόγραμμα άσκησης ενώ η θερμοκρασία διάλυσης θα μειωθεί κατά 1°C συγκριτικά με την κλασική θερμοκρασία. Τις ημέρες των αξιολογήσεων θα προσέλθετε στο νοσοκομειακό χώρο μισή ώρα νωρίτερα από την προκαθορισμένη ώρα αιμοκάθαρσης για να πραγματοποιηθούν κάποια λειτουργικά τεστ, ενώ στο τέλος της θα πρέπει να παραμείνετε στο νοσοκομειακό χώρο για άλλες 2 ώρες

προκειμένου να πραγματοποιηθούν κάποια λειτουργικά τεστ και η χορήγηση 75g γλυκόζης διαλυμένη σε 250-350ml νερού για να μπορέσει να γίνει η καμπύλη ζαχάρου. Η άσκηση που θα πραγματοποιηθεί κατά τη διάρκεια της αιμοκάθαρσης (τρίτη και τέταρτη αξιολόγηση) θα περιλαμβάνει ποδήλατο και ασκήσεις αντιστάσεων με βαράκια διάρκειας 40 λεπτών (20 λεπτά ποδήλατο + 20 λεπτά ασκήσεις με μαλακούς ιμάντες).

3. Κίνδυνοι και ενοχλήσεις

Κατά τη διάρκεια ή στο τέλος της προπονητικής παρέμβασης ίσως αισθανθείτε ήπια κόπωση, πιάσιμο των μυών σας, πόνο, σφίξιμο στο στήθος ή ζάλη. Σε πολύ σπάνιες περιπτώσεις μπορεί να σας παρουσιαστεί τάση για έμετο ή λιποθυμία. Για την αξιολόγηση της ανοχής της γλυκόζης θα γίνει λήψη φλεβικού αίματος, κατά τη διάρκεια της αιμοληψίας ίσως νιώσετε μία μικρή ενόχληση (τσίμπημα). Για την αξιολόγηση του φαιού λιπώδη ιστού θα σας ζητηθεί να απομακρύνεται για λίγα λεπτά τα ρούχα που καλύπτουν το άνω μέρος του σώματος σας. Η μέτρηση θα περιλαμβάνει την φωτογράφηση του άνω μέρους του σώματος σας με μια ιδική θερμική κάμερα που θα καταγράψει την θερμοκρασία του σώματος σας σε διάφορα σημεία και όχι τα χαρακτηριστικά σας. Για την ορθή αξιολόγηση της θερμοκρασίας σώματος θα σας δοθεί μια κάψουλα (υπό μορφή πολυβιταμίνης) την οποία θα πρέπει να λάβετε 6-8 ώρες πριν την έναρξη της αιμοκάθαρσης (πριν πάτε για ύπνο), η χρήση αυτής της κάψουλας είναι ασφαλής και δεν φέρει αντενδείξεις. Η προσεκτική παρακολούθηση σας κατά τη διάρκεια του προγράμματος άσκησης και των δοκιμασιών αξιολόγησης θα ελαχιστοποιήσουν τις πιθανότητες εμφάνισης κάποιου κινδύνου για τον οργανισμό σας. Διαθέσιμος εξοπλισμός και ειδικευμένο προσωπικό θα είναι στη διάθεση σας για την αντιμετώπιση οποιουδήποτε κινδύνου .

4. **Προσδοκώμενες ωφέλειες**

Το πρόγραμμα άσκησης που θα ακολουθήσετε θα έχει ως στόχο τη βελτίωση της φυσική σας κατάστασης και της λειτουργικότητας σας στην εκπλήρωση των καθημερινών σας δραστηριοτήτων και υποχρεώσεων. Η επανάληψη των δοκιμασιών αξιολόγησης θα μας δώσουν μια σαφέστερη εικόνα των προσαρμογών που παρατηρούνται στα πλαίσια της ερευνητικής παρέμβασης. Επίσης θα λάβετε δωρεάν αποτελέσματα και σημαντικές πληροφορίες για το λειτουργικό σας προφίλ από εξετάσεις που στο εμπόριο κοστίζουν >100 ευρώ.

5. Δημοσίευση δεδομένων – αποτελεσμάτων

Η συμμετοχή σας στην έρευνα συνεπάγεται ότι συμφωνείτε στην μελλοντική δημοσίευση των αποτελεσμάτων της, με την προϋπόθεση ότι οι πληροφορίες θα είναι ανώνυμες και δε

θα αποκαλυφθούν τα ονόματα των συμμετεχόντων. Τα δεδομένα που θα συγκεντρωθούν θα κωδικοποιηθούν με αριθμό, για την προστασία των προσωπικών σας δεδομένων.

6. Πληροφορίες

Για οποιαδήποτε αμφιβολία ή απορίες σχετικά με τις δοκιμασίες αξιολόγησης και το πρόγραμμα άσκησης μπορείτε να υποβάλλετε τις ερωτήσεις σας και τους προβληματισμούς σας απευθείας σ' εμάς για περαιτέρω πληροφορίες. Να έχετε υπόψη σας και να θυμάστε ότι είστε ελεύθεροι να αποσυρθείτε οποιαδήποτε στιγμή επιθυμητέ από το πρόγραμμα άσκησης.

7. Ελευθερία συναίνεσης

Η συμμετοχή σας στην εργασία είναι εθελοντική. Είστε ελεύθερος-η να μην συναινέσετε ή να διακόψετε τη συμμετοχή σας όποτε το επιθυμείτε. Στο τέλος των 4 παρεμβάσεων θα αποζημιωθείτε για τα πιθανά έξοδα σας με το ποσό των 100 ευρώ.

8. Δήλωση συναίνεσης

Διάβασα το έντυπο αυτό και κατανοώ τις διαδικασίες που θα ακολουθήσω. Συναινώ να συμμετάσχω στην ερευνητική εργασία.

Ημερομηνία: __/__/__

Ονοματεπώνυμο και υπογραφή
Υπογραφή ερευνητή
συμμετέχοντο _____

_____

Ονοματεπώνυμο και υπογραφή

παρατηρητή: _____

_____

Appendix 3: General Health Questionnaires

SF-36 ΕΡΕΥΝΑ ΥΓΕΙΑΣ

ΗΜΕΡΟΜΗΝΙΑ _____ **ΚΩΔΙΚΟΣ** _____

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
ζ. 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
Ηπιο 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 μεγαλύτερο διάστημα	Σημαντικό διάστημα	Μερικές φορές	Μικρό διάστημα	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 ΑΛΗΘΙΝΕΣ ή ΨΕΥΔΕΙΣ είναι οι παρακάτω προτάσεις στη δική σας περίπτωση; (κυκλώστε ένα αριθμό σε κάθε σειρά)

	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 γνωστοί 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

FATIGUE SEVERITY SCALE
[FSS]

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
_____										

Appendix 4: Copyright Statement

Υπεύθυνη Δήλωση

Η κάτωθι υπογεγραμμένη ΝΑΜΕ μεταπτυχιακή/ος φοιτήτρια/ης του Προγράμματος Μεταπτυχιακών 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 Μεταπτυχιακής Διπλωματικής Εργασίας (ΜΔΕ) μου με τίτλο «Η επίδραση της μυικής κόπωσης στην νευρομυική δραστηριότητα κατά τη διάρκεια του ύπνου»

(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: 22/04/2019

Η δηλούσα: Αργυρώ Κρασέ

Appendix 5: Protocol Registration – Clinical Trial.gov

ClinicalTrials.gov PRS
Protocol Registration and Results System

Home > Record Summary

ID: 921-5/11/2014 Impact of Cold Dialysis in Combination With Intradialytic Exercise in Aspects Related to Quality of Life and Health

Record Summary

Home Help

Record Status

In Progress ➡ Entry Completed ➡ Approved ➡ Released ➡ PRS Review ➡ Public

Reset to In-Progress...

Record Owner:	GSakkas	Access List:	[] Edit
Last Update:	04/04/2019 16:10 by QA37	Upload:	Allowed Edit
Initial Release:	03/29/2019	PRS Review:	Review History
Last Release:	04/04/2019 Receipt (PDF)	Public Site:	Last Public Release: 04/04/2019 View on ClinicalTrials.gov
		FDAAA:	Non-ACT (No FDA-regulated drug/device)

Spelling Preview Draft Receipt (PDF RTF) Download XML

Open **Protocol Section**

Identifiers: NCT03905551 Unique Protocol ID: 921-5/11/2014

Brief Title: Impact of Cold Dialysis in Combination With Intradialytic Exercise in Aspects Related to Quality of Life and Health (REACD)

Module Status:
- Study Identification: ✓
- Study Status: ✓
- Sponsor/Collaborators: ✓
- Oversight: ✓
- Study Description: ✓
- Conditions: ✓
- Study Design: ✓
- Arms and Interventions: ✓
- Outcome Measures: ✓
- Eligibility: ✓
- Contacts/Locations: ✓
- IPD Sharing Statement: ✓
- References: ✓

Open **Document Section**

Only certain studies need to have study documents uploaded.

- Full study protocol and statistical analysis plan -- required with results information submission for studies with a Primary Completion Date on or after January 18, 2017
- Informed consent forms - optional for all studies

Uploaded PDF/A Documents:

Results Section

Enter Results Results submission is required by FDAAA 801 for certain applicable clinical trials of drugs, biologics and devices. Note: other clinical trials may need to have results submitted based on other funder or sponsor policies.

Delay Results For applicable clinical trials subject to FDAAA 801, results submission may be delayed (in limited circumstances) with a Certification or Extension Request.

For more information see: When Do I Need to Register and Submit Results?

Add **Record Log**

Appendix 6 Supplementary results for the study 2

Table 4. Results and comparisons for functional capacity for each dialysis session

	Results for each protocol (mean±sd)				Post hoc comparisons between protocols (p-value[effect size])					
Time	**TD**	**CD**	**TD+E**	**CD+E**	**TD vs CD**	**TD vs TD+E**	**TD vs CD+E**	**CD vs TD+E**	**CD vs CD+E**	**TD+E vs CD+E**
Physical Performance Test										
				Six minute walking test (m)						
Pre	444.4±58.1	449.2±58.4	443.1±56.7	454.4±49.2	0.81[0.04]	0.89[0.02]	0.62[0.10]	0.33[0.10]	0.47[0.09]	0.19[0.20]
Post	435.5±66.3	438.6±48.2	427.1±52.8	436.8±50.2	0.77[0.05]	0.56[0.08]	0.78[0.05]	0.14[0.22]	0.69[0.03]	0.23[0.18]
				Six meter fast walking (sec)						
Pre	3.86±0.7	4.03±0.4	4.19±0.9	4.12±0.9	0.50[0.23]	0.08[0.35]	0.17[0.32]	0.52[0.20]	0.73[0.11]	0.48[0.07]
Post	4.48±1.1	4.25±0.5	4.29±1.0	4.37±1.1	0.34[0.24]	0.25[0.17]	0.53[0.09]	0.80[0.05]	0.59[0.13]	0.69[0.07]
				Sit to stand 5 repetitions						
Pre	12.68±8.0	11.30±5.3	13.76±11.5	12.46±6.2	0.48[0.13]	0.29[0.16]	0.85[0.03]	0.27[0.26]	**0.03**[0.19]	0.50[0.13]
Post	13.52±8.5	11.86±4.6	11.48±5.2	12.51±6.4	0.33[0.23]	0.14[0.28]	0.36[0.13]	0.54[0.07]	0.43[0.11]	0.16[0.17]
				Sit to Stand 60 seconds (sec)						
Pre	24.55±8.7	25.10±8.0	26.2±9.8	24.70±8.9	0.75[0.05]	0.95[0.01]	0.29[0.17]	0.45[0.[12]	0.64[0.04]	0.32[0.15]
Post	22.80±7.8	24.40±8.4	24.50±8.7	23.70±8.0	0.32[0.19]	0.36[0.20]	0.57[0.11]	0.88[0.01]	0.42[0.08]	0.47[0.09]
				Hand Grip (kg)						
Pre	29.52±8.1	31.07±9.8	29.22±13.2	31.29±9.6	0.47[0.15]	0.17[0.26]	0.39[0.16]	0.86[0.03]	0.77[0.02]	0.76[0.04]
1h	29.09±7.9	30.65±10.0	32.89±8.8	30.09±10.1	0.36[0.17]	0.18[0.29]	0.60[0.11]	0.61[0.09]	0.45[0.05]	0.55[0.11]
2h	30.27±9.2	30.42±10.4	32.26±8.0	30.39±10.1	0.91[0.01]	0.78[0.03]	0.93[0.01]	0.80[0.03]	0.95[0.00]	0.78[0.03]
3h	30.70±8.39	31.15±9.7	33.20±8.8	31.34±10.2	0.75[0.05]	0.57[0.09]	0.67[0.07]	0.48[0.07]	0.82[0.02]	0.80[0.02]
4h	30.78±9.7	30.82±10.9	33.08±8.77	30.07±9.54	0.98[0.00]	0.72[0.03]	0.49[0.08]	0.82[0.03]	0.08[0.08]	0.25[0.15]
Post	29.49±7.66	31.49±8.27	31.80±6.34	30.11±8.18	**0.03**[0.24]	0.15[0.16]	0.37[0.07]	0.28[0.17]	0.15[0.16]	0.63[0.08]

Note: Post hoc tests indicate comparisons between different protocols at the same time point.

Table 2. Results and comparisons for insulin sensitivity parameters for each dialysis session

Results for each protocol (mean±sd)				Post hoc comparisons between protocols (p-value[effect size])					
TD	**CD**	**TD+EX**	**CD+EX**	**TD vs CD**	**TD vs TD+EX**	**TD vs CD+EX**	**CD vs TD+EX**	**CD vs CD+EX**	**TD+EX vs CD+EX**
OGIS (ml·min^{-1}·m^{-2})									
499.1±92.5	502.4±74.8	508.5±84.3	522.7±82.7	0.87[0.04]	0.64[0.10]	0.81[0.33]	0.32[0.07]	0.68[0.25]	0.75[0.07]
Rate of Glucose (mg/dl/min)									
171.0±28.8	155.6±30.5	156.5±29.6	159.0±33.1	**0.07[0.50]**	**0.07[0.48]**	0.38[0.37]	0.34[0.03]	0.76[0.10]	0.82[0.11]
Rate of Insulin (mg/dl/min)									
61.6±27.5	48.5±24.0	40.3±18.3	52.9±26.5	0.29[0.48]	**0.09[0.85]**	0.43[0.31]	0.26[0.36]	0.90[0.16]	0.14[0.36]

Note: Post hoc tests indicate comparisons between different protocols at the same time point. P<0.05

Table 3. Results and comparisons for arterial pressure, No_2, heart rate and O_2 for each dialysis session

	Results for each protocol (mean±sd)				Post hoc comparisons between protocols (p-value[effect size])					
Time	**TD**	**CD**	**TD+E**	**CD+E**	**TD vs CD**	**TD vs TD+E**	**TD vs CD+E**	**CD vs TD+E**	**CD vs CD+E**	**TD+E vs CD+E**
Systolic Blood Pressure (SP)										
Pre	130.9±16.7	135.9±24.6	138.7±26.6	128.0±20.8	0.32[0.23]	0.19[0.34]	0.66[0.15]	0.32[0.10]	0.39[0.33]	0.28[0.43]
1h	119.8±13.5	121.5±26.9	119.8±18.4	123.5±34.0	0.76[0.08]	1.00[0.00]	0.65[0.14]	0.68[0.07]	0.65[0.06]	0.56[0.13]
2h	121.0±18.0	123.2±32.9	122.8±22.9	116.8±29.8	0.71[0.08]	0.73[0.08]	0.39[0.16]	0.93[0.01]	**0.03**[0.20]	0.20[0.22]
3h	118.1±22.9	123.3±27.2	121.1±25.8	115.6±29.0	0.26[0.20]	0.57[0.12]	0.62[0.09]	0.60[0.08]	**0.02**[0.26]	0.29[0.19]
4h	119.6±30.3	124.6±33.0	119.4±28.9	117.9±31.4	0.31[0.15]	0.95[0.01]	0.77[0.05]	0.23[0.16]	0.22[0.20]	0.79[0.05]
Post	120.1±25.5	130.0±31.3	124.3±31.2	118.7±31.4	**0.03**[0.33]	0.29[0.14]	0.78[0.05]	0.33[0.17]	**0.01**[0.35]	0.41[0.17]
Diastolic Blood Pressure (DP)										
Pre	70.6±13.9	75.7±9.84	73.8±15.2	74.3±12.2	0.08[0.41]	0.20[0.21]	0.14[0.27]	0.59[0.14]	0.60[0.12]	0.85[0.03]
1h	68.2±11.5	66.8±13.4	70.3±12.4	68.6±14.5	0.45[0.11]	0.25[0.17]	0.88[0.03]	0.21[0.26]	0.46[0.12]	0.56[0.12]
2h	69.4±12.1	72.0±12.1	71.4±10.6	67.3±14.7	0.12[0.20]	0.30[0.17]	0.33[0.15]	0.65[0.05]	**0.02**[0.33]	0.14[0.31]
3h	66.3±12.9	71.4±12.6	73.4±11.7	67.0±13.4	0.09[0.38]	0.09[0.55]	0.82[0.05]	0.52[0.16]	0.18[0.32]	0.06[0.49]
4h	66.7±9.2	74.2±12.7	66.4±14.2	70.8±14.1	**0.01**[0.64]	0.92[0.02]	0.18[0.33]	**0.01**[0.55]	0.32[0.24]	0.25[0.30]
Post	69.9±10.3	68.6±9.2	70.0±11.9	68.7±14.6	0.46[0.13]	0.96[0.01]	0.69[0.09]	0.54[0.13]	0.97[0.01]	0.74[0.09]
Nitrogen Dioxide (No_2)										
Pre	4.6±9.3	2.8±4.6	6.4±10.6	7.2±9.0	0.25[0.15]	0.27[0.55]	0.30[0.30]	0.37[0.44]	0.80[0.10]	0.91[0.06]
1h	4.5±7.7	2.0±2.8	6.0±6.8	5.7±9.8	0.72[0.18]	0.89[0.04]	0.71[0.05]	0.21[0.62]	0.27[0.58]	0.41[0.37]
2h	4.6±6.5	3.8±9.0	3.2±5.9	6.0±9.3	0.74[0.10]	0.70[0.11]	0.49[0.20]	1.00[0.00]	0.79[0.05]	0.54[0.29]
3h	4.7±5.0	5.0±9.6	3.2±4.7	6.4±9.8	0.83[0.10]	0.26[0.39]	0.75[0.15]	0.72[0.20]	0.47[0.18]	0.51[0.35]
4h	3.6±5.3	3.5±5.5	4.1±4.4	5.7±7.4	0.84[0.12]	0.85[0.13]	0.86[0.10]	0.94[0.03]	1.00[0.00]	0.69[0.22]
Post	5.1±5.9	4.0±5.9	2.8±3.7	5.5±5.9	0.76[0.19]	0.45[0.35]	0.77[0.14]	0.83[0.09]	0.92[0.04]	0.41[0.47]
Heart Rate (bpm)										
Pre	67.9±14.2	68.0±15.2	69.3±13.6	68.1±12.6	0.94[0.01]	0.79[0.10]	0.96[0.01]	0.81[0.09]	0.98[0.01]	0.57[0.09]
1h	68.8±14.6	70.0±13.6	70.3±14.5	71.5±14.8	0.70[0.04]	0.96[0.01]	0.26[0.17]	0.94[0.02]	0.55[0.10]	0.79[0.08]
2h	73.4±17.9	69.1±13.7	76.1±19.5	78.7±16.4	0.14[0.26]	0.74[0.09]	0.11[0.30]	0.30[0.38]	**0.00**[0.61]	0.64[0.13]
3h	73.8±18.7	69.2±16.9	75.4±17.8	73.9±15.3	0.37[0.14]	0.77[0.08]	0.98[0.01]	0.37[0.30]	0.26[0.26]	0.66[0.09]
4h	77.2±19.1	75.6±18.9	75.2±17.2	72.4±16.9	0.70[0.08]	0.62[0.11]	0.34[0.27]	0.90[0.03]	0.56[0.20]	0.33[0.16]
Post	69.2±14.5	72.2±13.8	71.5±12.7	69.6±14.0	0.32[0.20]	0.63[0.16]	0.96[0.03]	0.84[0.05]	0.45[0.18]	0.31[0.14]
Oxygen Saturation (%)										
Pre	97.5±1.3	98.2±1.1	96.9±2.8	97.0±2.3	**0.05**[0.54]	0.36[0.26]	0.41[0.25]	0.22[0.58]	0.14[0.63]	0.86[0.04]
1h	96.7±1.1	98.1±0.9	97.0±1.3	97.0±1.5	**0.02**[1.23]	0.53[0.31]	0.40[0.29]	**0.01**[0.90]	**0.06**[0.72]	0.84[0.07]
2h	98.1±0.8	97.9±1.6	97.1±1.6	96.5±2.8	0.83[0.09]	**0.03**[0.79]	0.17[0.69]	0.13[0.61]	0.15[0.53]	0.61[0.24]
3h	97.7±1.2	98.2±1.0	96.8±2.7	97.0±2.4	0.11[0.68]	0.40[0.46]	0.41[0.40]	0.14[0.79]	0.17[0.60]	0.08[0.34]
4h	97.7±1.0	98.1±1.1	96.6±1.8	97.2±2.6	0.31[0.43]	**0.04**[0.86]	0.36[0.34]	**0.01**[1.35]	0.40[0.41]	0.17[0.46]
Post	98.2±0.6	98.2±1.0	97.7±1.6	97.7±1.2	1.00[0.00]	0.51[0.39]	0.37[0.51]	0.24[0.28]	0.37[0.35]	0.69[0.00]

Note: Post hoc tests indicate comparisons between different protocols at the same time point.

Appendix 7. Published paper related to the Literature review

World Journal of Nephrology

Submit a Manuscript: http://www.f6publishing.com

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MINIREVIEWS

Cold dialysis and its impact on renal patients' health: An evidence-based mini review

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Abstract

Chronic renal disease is associated with advanced age, diabetes, hypertension, obesity, musculoskeletal problems and cardiovascular disease, the latter being the main cause of mortality in patients receiving haemodialysis (HD). Cooled dialysate (35 ℃-36 ℃) is recently employed to reduce the incidence of intradialytic hypotension in patients on chronic HD. The studies to date that have evaluated cooled dialysate are limited, however, data suggest that cooled dialysate improves hemodynamic tolerability of dialysis, minimizes hypotension and exerts a protective effect over major organs including the heart and brain. The current evidence-based review is dealing with the protective effect of cold dialysis and the benefits of it in aspects affecting patients' quality of care and life. There is evidence to suggest that cold dialysis can reduce cardiovascular mortality. However, large multicentre randomized clinical trials are urgently needed to provide further supporting evidence in order to incorporate cold dialysis in routine clinical practice.

Key words: Mortality; Cardiovascular diseases; Fatigue; Hypotension; Shivering; Renal failure

Core tip: Cooled dialysate (35 ℃-36 ℃) is recently employed to reduce the incidence of intradialytic hypotension in patients on chronic haemodialysis. The studies to date that have evaluated cooled dialysate are limited, however, data suggest that cooled dialysate improves hemodynamic tolerability of dialysis and exerts a protective effect over major organs. There is evidence