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Exercise as a Protective Cardiovascular Factor in ESRD Patients

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Abstract

Objective: The aim of the study was to show the effectiveness of Physical Activity (PA) during dialysis as a protective treatment against cardiovascular (CV) diseases.

Methods: Eighty volunteer patients were included in this multicentric prospective study and followed for one year: 40 patients in the Exercise group (EX), 40 patients in the Control group (CON). CV risk factors: Total Cholesterol, HDL Cholesterol (HDL-c), LDL cholesterol (LDL-c), Triglycerides (TG) and Hemoglobin (Hb), were checked. The number of antihypertensive treatments and the Erythropoietin Stimulating Agent (ESA) required doses were collected. We noted for each group during the follow-up the number of hospitalizations for CV reasons.

Results: We observed a slight decrease of total cholesterol in both groups, more important for EX (1.82 ± 0.47 at M0 (Month 0), 1.74 ± 0.51 at M12 (Month 12) than for CON (1.60 ± 0.26 at M0; 1.63 ± 0.45 at M12). HDL-c increased in both groups, but LDL-c decreased in EX and increased in CON. The TG decreased in both groups after one year. The Hb level remained more stable in the EX group (11.70 ± 1.17 to 12.06 ± 1.11, $p < 0.05$) than in the CON group (11.79 ± 1.01 (M0) and 11.35 ± 1.21 (M12)). There was a significant difference between EX and CON at M12 (respectively 12.06 ± 1.11 vs. 11.35 ± 1.21). At the same time, the required doses of Erythropoietin Stimulating Agent (ESA) decreased in EX and increased in CON. The number of antihypertensive drugs per patient decreased significantly ($p < 0.05$) in the EX group between M0 and M12 (1.85 ± 1.08 at M0 and 1.55 ± 0.85 at M12). The EX patients were 3 times less frequently hospitalized for cardiovascular reasons. There were 3 hospital stays versus 20 for the CON group.

Conclusion: Our study demonstrates that an intradialytic aerobic cycling training program promotes beneficial effects on cardiovascular protection: Lipids control, HTA control and Hb stability. Physical Activity although reduced the CV events in our population during one year follow-up.

Keywords: Chronic kidney disease; Exercise training; Cardiovascular protection

Introduction

Cardiovascular (CV) Diseases, Chronic Kidney Disease (CKD) and Diabetes are among the main causes of death all over the world [1]. Between 1990 and 2010, the total number of deaths due to CV diseases increased by 25%, while the deaths caused by CKD and diabetes doubled [2]. CKD patients are at high risk of CV diseases, their leading cause of mortality [3,4]. CKD, this serious and prevalent pathology may be caused by Hypertension (HTA) and diabetes, but at the same time, may lead to secondary HTA, diabetes and/or metabolic syndrome. Although the prevalence of those traditional CV risk factors is elevated (HTA, diabetes, low HDL…) in ESRD (End-Stage Renal Disease) patients, other "nontraditional" CV risk factors have been identified such as: increased Oxidative stress (OS), inflammation, prothrombotic factors, cachexia and malnutrition [5-11]. Thus, many different co-morbid diseases can appear and create a vicious circle that leads to gradual inactivity which in turn may reduce physical functioning and increase mortality [12].

To reduce CKD progression and to decrease its associated disorders, few strategies are available. In chronic diseases, such as overweight, obesity and diabetes, there is proven evidence of beneficial effects of physical training [13]. The same beneficial effects were found for CKD patients in a meta-analysis published in 2011 including 1,863 patients in 45 interventional studies [14]. Many studies were published since, most of them demonstrating that Physical Activity (PA) improves physical functioning and quality of life [15,16]. Johansen et al. [17] suggested that the same recommendations published by the American College of Sport Medicine and the American Heart Association [18] for adults from 50 to 64 and those 65 and older suffering from chronic disease with or without functional limitation, should be applied to CKD patients. Many studies have shown the efficacy of PA for ESRD patient's cardiovascular protection such as HTA control, decrease of vascular lesions and improvement of VO_2 max [17-20]. PA has also a protective role against risk factors such as inflammation [21] and oxidative stress [22,23]. The efficacy of regular PA in ESRD patients improves their outcome [24-26]. The question is how to integrate PA in ESRD usual care [25-27].

Since 2012, we began a program of physical activity during dialysis for haemodialysis patients in all dialysis units of Auvergne, a region of France. With the approval of their nephrologists, of the 400 haemodialysis patients 150 have been included in this program and followed by our sport's teacher. Patients who practiced twice or three times a week have a continuous favourable clinical evolution. After 3 months of exercise in a randomized protocol, we showed improvements of lipid profile and reduction of pro-oxydants (Isoprostane) [23]. After 6 months of regular exercise during dialysis, we showed that the lipid profile was improved, the number of hypertensive treatment was reduced and the ratio hospitalization for cardiovascular reason per total hospitalization was lowered. Our aim in the current study was to explore the effects in patients who practice exercise during dialysis after one year.

Materials and Methods

This prospective, multicentre study was conducted between April

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2014 and April 2015 in Auvergne. Eighty haemodialysis patients in all dialysis units in Auvergne volunteered to be participant in this study. We matched 40 patients in the Exercise group (EX) with 40 control patients (CON). The patients included in the EX group underwent a 12-months intradialytic aerobic exercise training program consisting of cycling 2 to 3 days a week for 20/30 minutes on specialized cycle ergometers (oxyCycle II). The cycles were adapted to the patient's dialysis chair or bed. Each patient determined its own work rate; they cycled between 40 to 80 rpm without resistance.

We followed the patients as usual and collected the number of antihypertensive treatments, the Erythropoietin Stimulating Agent (ESA) required doses, the Haemoglobin level (Hb) and the Lipid profile: Total Cholesterol, HDL cholesterol (HDL-c), LDL cholesterol (LDL-c), Triglycerides (TG). We checked every hospitalization for cardiovascular reasons including pulmonary oedema, infarcts, peripheral ischemia, necrosis, and amputation for vascular reasons, vascular angioplasties, and any perturbation of the heart rhythm during one year.

Concerning the Erythropoietin Stimulating Agent (ESA) doses, we used a conversion table from Epoietin alpha and Darbepoietin alpha to a monthly dose of Methoxy Polyethylen Glycol Epoietin beta.

Statistical analysis

Values for the continuous variables are expressed as mean ± standard deviation (SD). All statistical analyses were performed using the Statistica 7.1 software. Two-way ANOVA was used after checking the binomial probability distribution and variance. The post-hoc Tukey analysis was used when the interaction was significant. The significant level adapted was 0.05.

Results

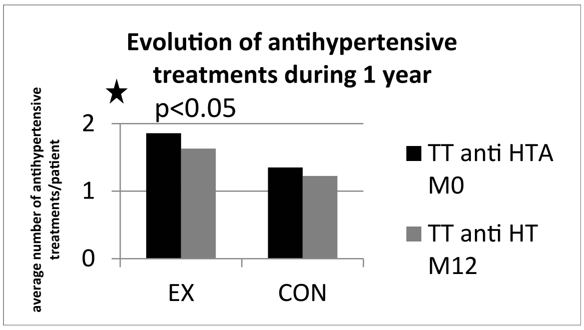
The mean age in the EX group was 66.8 ± 10.6 years and 67.65 ± 13.4 years in the CON group. There were more males in the EX group: 67.5% versus 57.5%.

No difference was reported between the two groups concerning age, Charlson comorbidity index or time in dialysis, as listed in Table 1. There were more male in EX and they had more cardiovascular history. The numbers of diabetic and hypertensive patients were comparable. We found no significant difference for the sodium and fluid intakes between the 2 groups at the beginning of the study. During the follow-up, we had no withdrawals in the two groups.

The number of antihypertensive treatments were lowered significantly ($p < 0.05$) in the EX group between M0 (Month 0) and M12 (Month 12) (1.85 ± 1.08 at M0 and 1.55 ± 0.85 at M12) (Figure 1). In the CON group we observed a non-significant trend toward fewer needs of drugs (from 1.35 ± 1.02 to 1.22 ± 1.02) (Table 1).

With respect to anaemia we found that Hb remained more stable for the EX group: 11.70 ± 1.17 to 12.06 ± 1.11, $p < 0.05$ than in the CON group: 11.79 ± 1.01 to 11.35 ± 1.21 at M12 (Figure 2). We observed a significance difference between EX and CON at M12 (respectively 12.06 ± 1.11 *vs* 11.35 ± 1.21). While Hb remained stable, the required ESA doses decreased in EX and increased in CON, but not significantly (Figure 3).

For the lipids, we found no significant change (Table 2). We observed a slight decrease of total cholesterol in both groups, more important for the EX (1.82 ± 0.47 at M0, 1.74 ± 0.51 at M12) than for the CON (1.60 ± 0.26 M0 1.63 ± 0.45 M12). The HDL-c increased in both groups, but



*Significant difference between M0 and M12 in EX; p < 0.05
Figure 1: Evolution of the number of antihypertensive treatments / patient.

	CON (n=40)		EX (n=40)	
	M0	M12	M0	M12
Age (years)	67.65 ± 13.4		66.8 ± 10.6	
Gender	23m, 17f		27m, 13f	
Charlson comorbidity index	5.22		5.23	
Ischemic cardiopathy	3 (7.5%)		7 (17.5%)	
Diabetes	12 (30%)		12 (30%)	
Hypertension	33 (82.5%)		34 (85%)	
Anti HTA treatments	1.35 ± 1.02	1.22 ± 1.02	1.85 ± 1.08	1.55 ± 0.85*
Salt Intake (g/day)	5.59 ± 1.36		5.33 ± 2.29	
Fluid Intake (ml/day)	1068.10 ± 82.66		972.11 ± 44.96	
Hemoglobin (g.dl-1)	11.79 ± 1.01	11.35 ± 1.21	11.70 ± 1.17	12.06 ± 1.11**
ESA required doses	89.63 ± 77.3	120 ± 155.7	110.83 ± 70.8	103.06 ± 57.3
Time on dialysis (months)	63.6 ± 11.31		63.4 ± 3.53	
Dialysis prescription (h/week)	12.11 ± 0.08		12.38 ± 1.41	

Values are mean ± SD; CON: Control group; EX: exercising-group
*Difference between M0 and M12, p < 0.05
**Difference between EX and CON at M12, p< 0.05
Table 1: Patient characteristics.

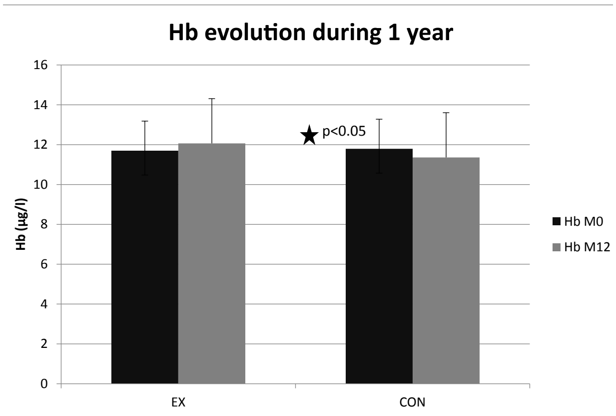
LDL-c decreased in EX and increased in CON, but not significantly.

The TG was higher at M0 in CON. It decreased in both groups after one year.

We collected all the hospitalizations for any cardiovascular cause. During the follow-up, the EX patients were less frequently hospitalized: 3 hospital stays (1 pulmonary oedema, 1 atrial fibrillation, 1 stroke) versus 20 for the CON group (7 heart rhythm troubles, 4 vascular angioplastia, 4 pulmonary oedema, 3 infarcts, 1 amputation, 1 stroke) (Table 3).

Discussion

Our study showed that an intradialytic aerobic cycling program exerts beneficial effects on HTA control, Lipid Profile and Anemia control in ESRD patients. Furthermore, this study is the first to report a significant difference between trained and untrained patients at the end of the intervention protocol concerning hospitalization for cardiovascular events.



*Significant difference at M12 between EX and CON; $p < 0.05$

Figure 2: Hb evolution.

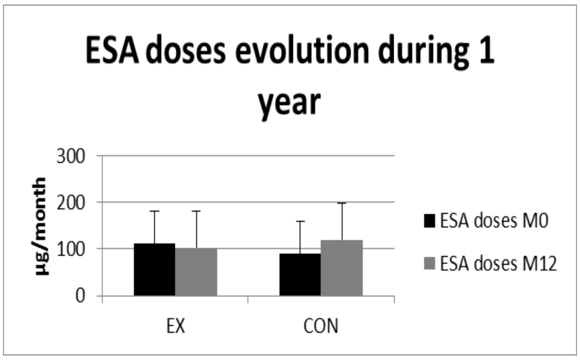


Figure 3: ESA doses evolution.

	CON (n=40)		EX (n=40)	
	M0	M12	M0	M12
Total Cholesterol (mg.dl-1)	1.60 ± 0.26	1.63 ± 0.45	1.82 ± 0.47	1.74 ± 0.51
HDL-c (g.l-1)	0.43 ± 0.1	0.46 ± 0.13	0.5 ± 0.17	0.51 ± 0.24
LDL-c (g.l-1)	0.88 ± 0.36	0.94 ± 0.35	1.02 ± 0.49	0.88 ± 0.49
TG (g.l-1)	1.70 ± 0.74	1.59 ± 0.88	1.63 ± 0.89	1.59 ± 1.13

Values are mean ± SD; CON: control group; EX: exercising-group

Table 2: Lipid profile.

The effects of exercise training on lipid profile and HTA control

The training program reduced plasma TG level (-14%), reduced LDL-c level (-12%) and raised HDL-c by 23%. Our results are similar to Goldberg et al. in 1983. In a similar training protocol during 9 months with 6 patients, they found that plasma TG level decreased by 39% and HDL-c increased by 16%. Fifty of these patients had a decrease in their antihypertensive drugs [28]. In our study, the number of antihypertensive treatments was significantly reduced between M0 and M12 in EX. It was also reduced by exercise in the study by Millers, but the HTA seemed to increase after the training protocol [29]. The education of patients is so important involving them in their treatment integrating PA.

Hb stability and decrease of ESA doses

CKD leads to decrease in erythropoietin synthesis. Haemodialysis patients have few endothelial progenitor cells and an unfavourable cardiovascular outcome [28,30]. It is well-known that the variation of Hb is now a cardiovascular risk factor [31]. In clinical practice, the anaemia correction with an ESA during CKD must ideally be slow and progressive. The morbidity due to quick variations of Hb has been intensively studied [31,32]. Hb stability in haemodialysis patients is a daily problem for the nephrologist. In our study Hb is more stable with lower doses of ESA with a regular PA. For Goldberg et al. Hb increased from 7 to 9 g/dl after the training period. They did not specify the ESA doses [28].

We showed a significant difference at M12 between EX and CON with lower doses of ESA.

Cardiovascular hospitalization

Many studies have shown beneficial effects of training on cardiovascular parameters.

Deligiannis et al. demonstrated that PA during 6 months of home training improves the left ventricular function [33]. A cross over prospective study with 19 haemodialysis patients who practiced per dialytic AP for 3 months showed that the pulse pression was better and the Brain Natriuretic Protein (BNP) decreased. The authors concluded that arterial compliance was improved [34]. Furthermore, HD patients suffer from cardiac dysfunction. It leads to a poor Baro Reflex Sensitivity (BRS), which may reduce respiratory and cardiac capacities. This low BRS has been associated with ventricular arrhythmia and sudden death in HD patients. Exercise during dialysis increases the BRS activity related to their functional capacity [35,36]. All those factors, associated with a better lipid control and a better HTA control can explain the decrease in hospitalization for CV reasons in our follow up.

Training program

We are involved in an educational program of intradialytic cycling protocol. It allows good compliance from patients when nurses and technicians are well informed and involved in this treatment. Exercise improves patients' monitoring and provides motivation in a structured environment. The time spent on hemodialysis is a period of forced inactivity which contributes to further degradation of physical functions. An intradialytic training program during this period reduces side effects of inactivity and increases exercise-induced positive effects. All the advantages of intradialytic training have been discussed by Cheema et al. [10] who recommended its incorporation into routine dialysis care. In our follow up, no subject dropped out of the protocol. This high degree of approval was probably due to the playful effect of aerobic exercise during the dialysis, the zest for the activity, the social aspect (some patients shared the same exercise session) and the positive effects on health. We propose to our hemodialysis patients and peritoneal dialysis patients that they participate to an exercise course during "day off dialysis" with our sport's teacher. The adherence was low for HD patients, but 30% of PD patients were faithful to the program.

Conclusion

The main objective of the therapeutic management of CKD subjects (including ESRD patients) is to delay the progress of the disease [30] and to prevent CV complications [38,39]. Our study demonstrated that an intradialytic aerobic cycling training program had beneficial effects on cardiovascular protection for HD patients. Intradialytic aerobic cycling training represents a useful and easy strategy to reduce CKD associated disorders. It involves all the care-givers: nurses, technicians and nephrologists to encourage and support the patients. Most important is to maintain the rhythm and continue the training. This education program requires the implication of all the team involved in CKD.

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