A Six-Month Intradialytic Exercise Programme has Anti-Inflammatory effects on Circulating Monocyte Phenotypes and Regulatory T cells but not on Cytokine Concentration.

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Background

Haemodialysis (HD) patients have a dysfunctional and chronically activated immune system :

- Elevated circulating markers of inflammation;
- leucocyte populations biased toward pro-inflammatory and proatherogenic phenotypes;
- anergy to antigen challenge.

Systemic inflammation and increased numbers of pro-inflammatory intermediate monocytes are associated with cardiovascular disease.

Evidence from observational and exercise training studies in other populations suggest that regular exercise may have a beneficial anti-inflammatory effect.

The effect of regular intradialytic exercise on systemic inflammation is unclear in HD patients.

Some studies show reduced CRP with exercise training, while many others show no change.

No studies have investigated the effect of exercise on cellular sources of inflammation in HD patients.

Aims

To assess the effect of 6 months regular intradialytic exercise on circulating markers of inflammation, and pro-inflammatory and anti-inflammatory leucocyte phenotypes.

Methods

Subjects

HD patients were recruited from two HD units :

- 22 patients from a unit where exercise was offered during HD for 6 months;
- 16 patients from a non-exercising control HD unit.

Exercise Intervention

Exercising patients were encouraged to exercise during HD for up to 3x / wk and to aim for 30 min of cycling at a perceived exertion of “somewhat hard”.

Outcome Assessments

Physical function was assessed at baseline and after 6 months using the sit-to-stand 60 (STS 60).

Blood samples were taken prior to HD at 0, 3 and 6 months in both groups. Plasma CRP, IL-6 and TNF-α were measured via ELISA.

The numbers and proportions of classical ($CD14^{++}CD16^{-}$), intermediate ($CD14^{++}CD16^{+}$), and non-classical ($CD14^{+}CD16^{++}$) monocyte phenotypes and regulatory T cells (Tregs; $CD4^{+}CD25^{+}CD127^{low/-}$) were measured via flow cytometry (Figure 1).

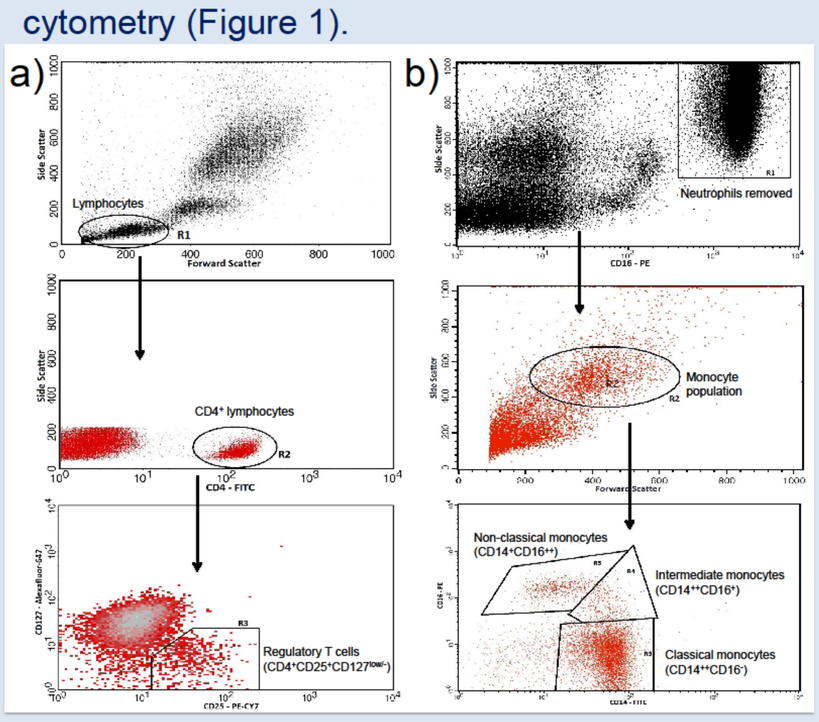

Figure 1. Flow cytometry analysis for (a) regulatory T cells, and (b) monocyte phenotypes

Results

Sixteen exercise and 15 control patients completed the 6-month study period (Table 1).

Table 1.	Exercise	Control
Age (y)	57.0 ± 10.5 y	70.2 ± 13.7
Gender (% Male)	50%	67%
HD vintage (y)	2.16 ± 1.65	2.71 ± 2.57

Six months of regular intradialytic exercise significantly improved STS 60 score in the exercise group (13 ± 10 to 24 ± 6 reps; $P < 0.001$, Figure 2) with no change in the control group.

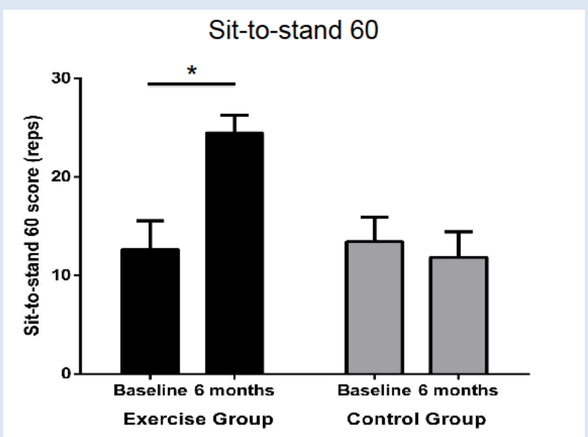

Figure 2. Physical function in exercise and control patients at baseline and after 6 months

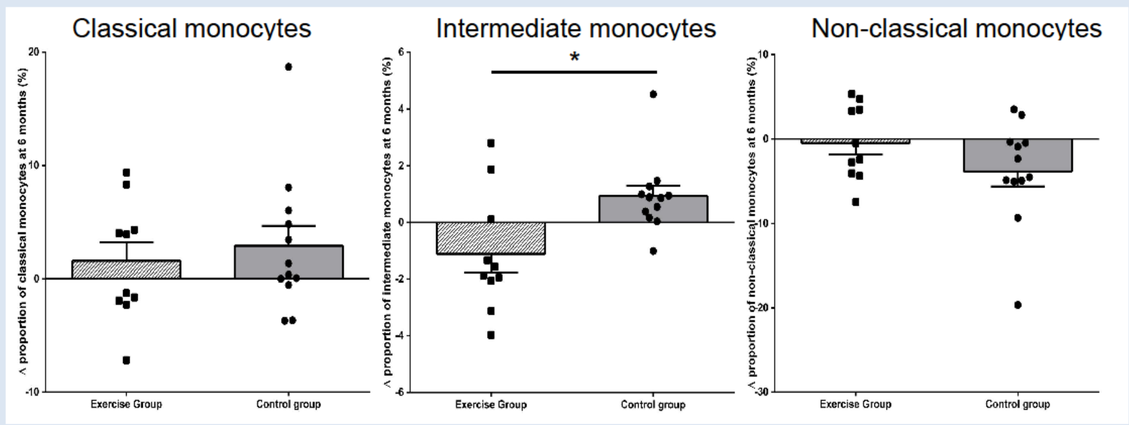

Figure 3. The change in the proportion of monocytes in a) classical, b) intermediate and c) non-classical phenotypes in exercise and control patients after 6 months

Monocyte phenotypes (Figure 3)

The exercise group had a significant decline in the proportion of monocytes that were the pro-inflammatory intermediate phenotype ($CD14^{++}CD16^{+}$) compared with the usual care group (7.72 ± 1.70 to 6.61 ± 1.74 % vs. 6.90 ± 1.56 to 7.82 ± 1.81 %; $P = 0.020$). No trends were observed in the classical or non-classical monocyte populations.

Cytokines (Table 2)

Training had no significant effect on circulating concentrations of CRP, IL-6 or TNF-α at 3 months or 6 months ($P \geq 0.411$, Table 2).

Regulatory T cells (Figure 4)

The number of the anti-inflammatory Tregs was enhanced after 6 months in the exercise group compared with the usual care group (28.1 ± 17.1 to 36.2 ± 17.3 cells/μL vs. 28.7 ± 13.2 to 22.4 ± 10.7 cells/μL; $P = 0.009$).

This may be explained by a greater number of total CD4+ lymphocytes compared with control ($P = 0.001$).

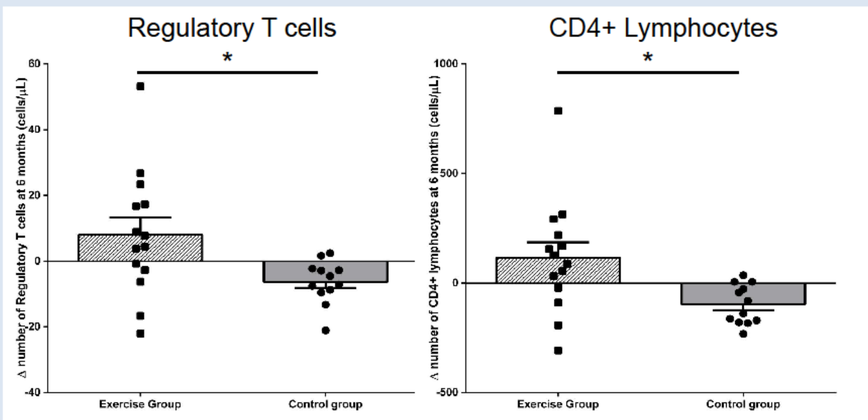

Figure 4. The change in the number of a) regulatory T cells, and b) CD4+ lymphocytes in exercise and control patients after 6 months

Table 2.	Exercise Group			Control Group		
	Baseline	3 months	6 months	Baseline	3 months	6 months
CRP (mg/L)	4.75 ± 3.38	3.63 ± 2.36	4.69 ± 3.42	6.93 ± 3.73	7.19 ± 3.48	7.96 ± 4.00
IL-6 (pg/mL)	5.34 ± 3.09	5.67 ± 2.85	5.90 ± 3.44	5.21 ± 2.71	5.71 ± 3.81	7.01 ± 5.08
TNF-α (pg/mL)	3.39 ± 1.17	3.50 ± 0.92	3.39 ± 1.16	4.55 ± 3.27	4.27 ± 1.95	4.21 ± 2.20

Conclusions

The present findings suggest that regular exercise has an anti-inflammatory effect at a circulating cellular level. Regular exercise during haemodialysis appears protective against the increased risk of CVD and mortality that is associated with chronic inflammation and elevated numbers of intermediate monocytes.

High levels of inter- and intra-individual variation in patients requiring haemodialysis may preclude the use of circulating cytokines in the detection of exercise training induced anti-inflammatory adaptations.

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