Acute aerobic session increased anti-inflammatory cytokine (IL-10) in CKD patients

A sessão aeróbica aguda aumentou a citocina anti-inflamatória (IL-10) em pacientes com CKD

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ABSTRACT
In patients with chronic kidney disease (CKD), the presence of inflammation is a predictor of mortality. The aerobic exercise has been described to modulate the inflammatory response in general population. However, CKD patients have some limitations to performed aerobic exercise frequently. Thus, the present study evaluated the effect of an acute aerobic exercise session on markers of inflammation in non-dialytic CKD patients. MATERIALS AND METHODS: 10 stage 3 CKD patients and 10 subjects with normal kidney function performed experimental sessions of aerobic exercise on a cycle ergometer for 45 min, 50% at VO2peak. Before and after the session, blood samples were collected for the analysis of IL-6, TNF-α, IL-10, CRP, NGAL and Cystatin C. The general linear model (GLM) test were used to evaluated the differences and interaction between group and time and Pearson's correlations were used to evaluate the association between the variables. RESULTS: Interestingly, after an aerobic exercise session, IL-10 levels increased in both group and more prominent in CKD group ($p < 0.0001$). As expected, CKD patients were more inflamed compared to the control group and IL-6 and TNF-α had a positive correlation with Cystatin-C and NGAL, markers of renal failure ($p < 0.001$). CONCLUSION: In this study, an acute aerobic exercise session was able to increase IL-10 levels in CKD patients, suggesting that acute aerobic exercise may contribute to an anti-inflammatory response. However, it is necessary future studies to evaluate the impact of increased IL-10 and acute aerobic exercise on outcomes in patients with CKD.

Keywords: *Acute Aerobic exercise, Inflammation, Chronic Kidney Disease*

RESUMO
Em pacientes com doença renal crônica (CKD), a presença de inflamação é um preditor de mortalidade. O exercício aeróbico tem sido descrito para modular a resposta inflamatória na população em geral. No entanto, os pacientes com CKD têm algumas limitações para realizar exercícios aeróbicos com freqüência. Assim, o presente estudo avaliou o efeito de uma sessão de exercício aeróbico agudo sobre os marcadores de inflamação em pacientes não dialíticos com CKD. MATERIAIS E MÉTODOS: 10 pacientes com CKD estágio 3 e 10 sujeitos com função renal normal realizaram sessões experimentais de exercício aeróbico em um cicloergômetro durante 45 min, 50% a VO2peak. Antes e depois da sessão, foram coletadas amostras de sangue para a análise de IL-6, TNF-α, IL-10, CRP, NGAL e cistatina C. O teste do modelo linear geral (GLM) foi usado para avaliar as diferenças e interação entre grupo e tempo e as correlações de Pearson foram usadas para avaliar a associação entre as variáveis. RESULTADOS: Curiosamente, após uma sessão de exercícios aeróbicos, os níveis de IL-10 aumentaram em ambos os grupos e mais proeminentes no grupo CKD ($p < 0,0001$). Como esperado, os pacientes com CKD estavam mais inflamados em comparação ao grupo controle e IL-6 e TNF-α tinham uma correlação positiva com cistatina C e NGAL, marcadores de insuficiência renal ($p < 0,001$). CONCLUSÃO: Neste estudo, uma sessão de exercício aeróbico agudo foi capaz de aumentar os níveis de IL-10 em pacientes com CKD, sugerindo que o exercício aeróbico agudo pode contribuir para uma resposta anti-inflamatória. Entretanto, são necessários estudos futuros para avaliar o impacto do aumento da IL-10 e do exercício aeróbico agudo nos resultados em pacientes com CKD.

Palavras-chave: Exercício aeróbico agudo, Inflamação, Doença Renal Crônica

1 INTRODUCTION

Chronic kidney disease (CKD) is characterized as an irreversible and progressive syndrome that reduces progressively kidney function, which may achieve complete failure (1). Actually, CKD is considered a global public health problem and the number of patients has increased exponentially (2, 3). According to world statistics, about 200 million people have some degree of CKD (4). This is due to the increase of risk factors for kidney disease, such as systemic arterial hypertension (SAH), diabetes mellitus (DM) and obesity (5-7). These traditional risk factors signalize inflammatory response that have impact on kidney filtration with a progressive loss of glomerular filtration rate (GFR)) (8, 9) and consequent high serum levels of filtration biomarkers as creatinine (10), cystatin C (11) and neutrophil gelatinase-associated lipocalin (NGAL) (12). Nowadays, NGAL have been recognized as an early biomarker of loss of renal function compared with creatinine (13).

CKD is a disease with high rate of morbidity and mortality (14). The decline of kidney function and the increase of the serum concentrations of uremic toxins; seem the main reason to signalize inflammatory response, resulting in damage of endothelial, vascular cells and high risk to mortality by cardiovascular diseases in CKD patients (15), besides to increase the injury renal. For this reason, some anti-inflammatory strategies therapeutic and non-therapeutics have been prescribed in CKD patients; mainly in pre-dialysis patients in an attempt to regulate mechanisms that contributed to the progression of kidney disease (16).

Despite some drugs therapy, as angiotensin-converting enzyme inhibitors 2 (17) (ACEI) and angiotensin-2 receptor blockers (ARBs) that are used as one of the medications to delay the progression of CKD (18); recently it has been recommended that CKD patients be encouraged to perform physical activities as an anti-inflammatory strategy.

In the general population, there are evidence that the practice of the exercise contribute to decrease of serum levels of inflammatory biomarkers (19, 20). Santos-Parker JR et al (21), reported that aerobic exercise diminished inflammation and improved endothelial function, however, the benefit of this type of the exercise on inflammation response are described for regular and frequent section, (at least 3 session/week) (20).

In CKD, it has been reported that sedentary patients have more risk to hospitalization and mortality (22). In contrast, Bohm et al ., 2017 (23) observed that hemodialysis patients that performed aerobic exercise continuously had increase of strength muscle mass, decrease of blood pressure and high production of antioxidants.

However, the regular practice of exercises in this population is not easy; because these patients have several difficulties as mobility, costs, time, need for caregiver among others.

Some studies in general population have shown that acute and moderate exercise session may promotes anti-inflammatory action soon after its completion, and in turn, the IL-6 it is the main cytokine involved in this modulation (24).

Although acute or moderate exercise session can exert influence of inflammatory responses in healthy individuals, it is still unclear the effect of acute aerobic exercise in patients with CKD (25). Thus, the objective of this study was evaluated the effect of an acute aerobic exercise session on kidney function biomarkers (NGAL and Cystatin-C) and inflammatory biomarkers (IL-6, 1L-10, TNF-α and CRP) in non-dialytic CKD patients.

2 MATHERIAL AND E METHODS

The sample size was performed with a confidence level of 95%, a margin of error of 5% and a Z score of 1.96, which indicated 80 individuals for the study. However due to the lack of adherence of patients with CKD to training, and loss of follow-up after the initial exercise test; we choosed 10 CKD patients as a sample size for convenience. To support, until moment, there are only two studies that studied the effects of acute exercise in CKD patients (Lau et al., 2015 (26) (sample size = 9) and Viana et al., 2014 (27) (sample size = 15).

We selected 10 stage 3 CKD patients (GFR >30 and < 51 mL/min) from the Nephrology Clinic of the University of São Paulo School of Medicine Hospital das Clínicas (HCFMUSP) and 10 healthy individuals with normal kidney function. After the individuals signed the free and informed consent (OPINION NUMBER ETHICS COMMITTEE: 797.505/ 17/09/2017, CAAE: 33073413.6.3001.0065) they were matched for gender, age and body mass index, were prepared, and directed to participate to the acute aerobic exercise session.

INCLUSION CRITERIA

CKD group: Patients with age ≥ 18 years and ≤ 70 years; GFR 30 to 51 mL/min; Bone Mass Index (BMI) below 35 kg / m2; Systolic Blood Pression (SBP) and Diastolic Blood Pression (DBP) below 160 and 105 mmHg, respectively. Absence of infection or inflammation in the last month, and without musculoskeletal, cardiovascular problems that would make it impossible the practice of aerobic exercise.

Control Group: Healthy subjects with age ≥ 18 years and ≤ 70 years; Creatinine Clearance (> 90 ml / min / 1.73m2); BMI below 35 kg / m2; SBP and DBP below 140 and 90 mmHg, respectively and absence of infection or inflammation in the last month, and without musculoskeletal, cardiovascular problems that would make it impossible the practice of aerobic exercise.

EXCLUSION CRITERIA

All individuals who presented complex or ischemic arrhythmias during the exercise test that contraindicated the performance of the activity or modified the drug treatment during the test period were excluded.

ACUTE AEROBIC EXERCISE SESSION

The subjects were instructed to eat a light meal two hours before the test and not to eat, on this day, any food containing caffeine. In addition, they were instructed not to perform physical exercises in the 48 hours preceding the test and not to drink alcohol in the previous 24 hours.

A 45-minute Cycle (Corival) exercise session was performed at 50% of VO2 peak, maintaining a speed of 60 rpm. This session was preceded by 7 minutes of rest sitting on the cycle ergometer and 3 minutes of warm-up with a power equivalent to 50% of that used during exercise. After exercise, an active recovery of 2 minutes was performed, and in the first minute the power was halved and in the second minute the power was zero. The protocol ended with 3 minutes of passive recovery in the sitting position on the cycle ergometer. To calculate the power required to reach 50% VO2 peak of each volunteer, the linear regression of the power and VO2 data obtained in the maximal exercise stress test previously performed was used.

INFLAMMATORY AND KIDNEY FUNCTION BIOMARKERS

The blood samples were collected before and after acute aerobic exercise session and were centrifuged and stored at -80^{o}C to analyse NGAL, Cystatin C, CRP, IL-6, TNF-α, IL-10 according to manufactures instructions. The Human ELISA kits used were: Human C-reactive protein/CRP DuoSet R&D Systems USA Lote: 336754 (PCR); Quantikine Immunoassay Human IL-6 HS R&D Systems USA Lote: P144049 (IL-6); Quantikine Immunoassay Human TNF-α HS (R&D Systems USA Lote: P141620 (TNF-α); Quantikine Immunoassay Human IL-10 HS R&D Systems USA Lote: P105705 (IL-

10); Quantikine Immunoassay Human Cystatin C R&D Systems USA Lote: 270844 (Cistatina C) e Quantikine Immunoassay Human Lipocalin-2/NGAL R&D Systems USA Lote: 271204 (NGAL).

STATISCAL ANALYSIS

Continuous data were initially compared to the normal curve by the Shapiro-Wilk test, and mathematical transformations were made when necessary. Parametric data were represented by mean and standard deviation, and nonparametric data as median and (IQ25-75%). Categorical data were described as absolute values and as a percentage of the total sample. To analyze the difference between groups and exercise responses on inflammation markers and renal function biomarkers, the General Linear Model (GLM) test was used to evaluated the interaction between Group *vs* Time and significance was considered when the p value <0.05. Pearson's or Spearman correlation test were used when appropriated to assess the association between inflammatory markers and renal function biomarkers exercise. The statistical software used was IBM SPSS STATISTICS 24.0.

3 RESULTS

Table 1: Descriptive and demographic data from control and CKD group

	CONTROL (n = 10)	**CKD (n = 10)**	**p**
Gender (female)	5 (50%)	6 (60%)	0.96
Age (years)	48 ± 6	55 ± 6	0.18
BMI (%)	23± 3	27 ± 4	0.60
Hypertension (%)	0 (0%)	10 (100%)	NA
DM (%)	0 (0%)	8 (80%)	NA
e-GFR (mL/min)	89 ±12	43 ± 9	< 0.05

BMI: Body Mass Index
DM: Diabetes mellitus
e-GFR: Estimated glomerular filtration rate
NA – not applicable
As expected, in Table 1, we can see that the only statistical difference between the groups CKD and Control is in the e-GFR: Estimated glomerular filtration rate.

Table 2: Pre and Post exercise effect on serum levels of IL-6, IL-10, TNF-alpha, CRP, NGAL and Cystatin C in CKD group compared to control group.

	CONT (N=10)			**CKD (N=10)**				
	Pre	**Post**	p#	**Pre**	**Post**	p*	pΔ	p†
IL6 (pg/mL)	**1.4 ± 0.4**	1.5 ± 0.5	0.56	**2.1 ± 0.4**	1.9 ± 0.4	0.2	**0.001**	0.11
IL10 (pg/mL)	28 (27– 38)	31 (30 - 43)	0.01	**32 (29 – 40)**	**40 (31 – 46)**	**0.001**	0.59	*0.29*
TNF-α (pg/mL)	**5.6 ± 1.1**	*5.6 ± 0.9*	0.9	**7.4 ± 1.2**	*7.6 ± 1.2*	0.7	**0.003**	*0.001*
CRP (mg/L)	0.6 (0.6 – 1.6)	0.6 (0.6 – 2.3)	0.2	1.7 (0.6 – 6.7)	1.8 (0.6 – 6.5)	0.9	0.07	0.08
NGAL (ng/mL)	**2.7 ± 0.8**	*2.7 ± 1*	0.9	**6.7 ± 2.4**	*6.4 ± 2.1*	0.4	**<0.001**	*<0.001*
Cyst-C (ng/mL)	**24 ± 11**	*29 ± 6*	0.14	**76 ± 22**	*81 ± 2*	0.2	**<0.001**	*<0.001*

$p^{\#}$: POST ≠ PRE (CONT)
p: POST ≠ PRE (CKD)*
p^{Δ}: PRE (CONT) ≠ PRE CKD
$p^{\dagger}$: POST (CONT) ≠ POST (CKD)

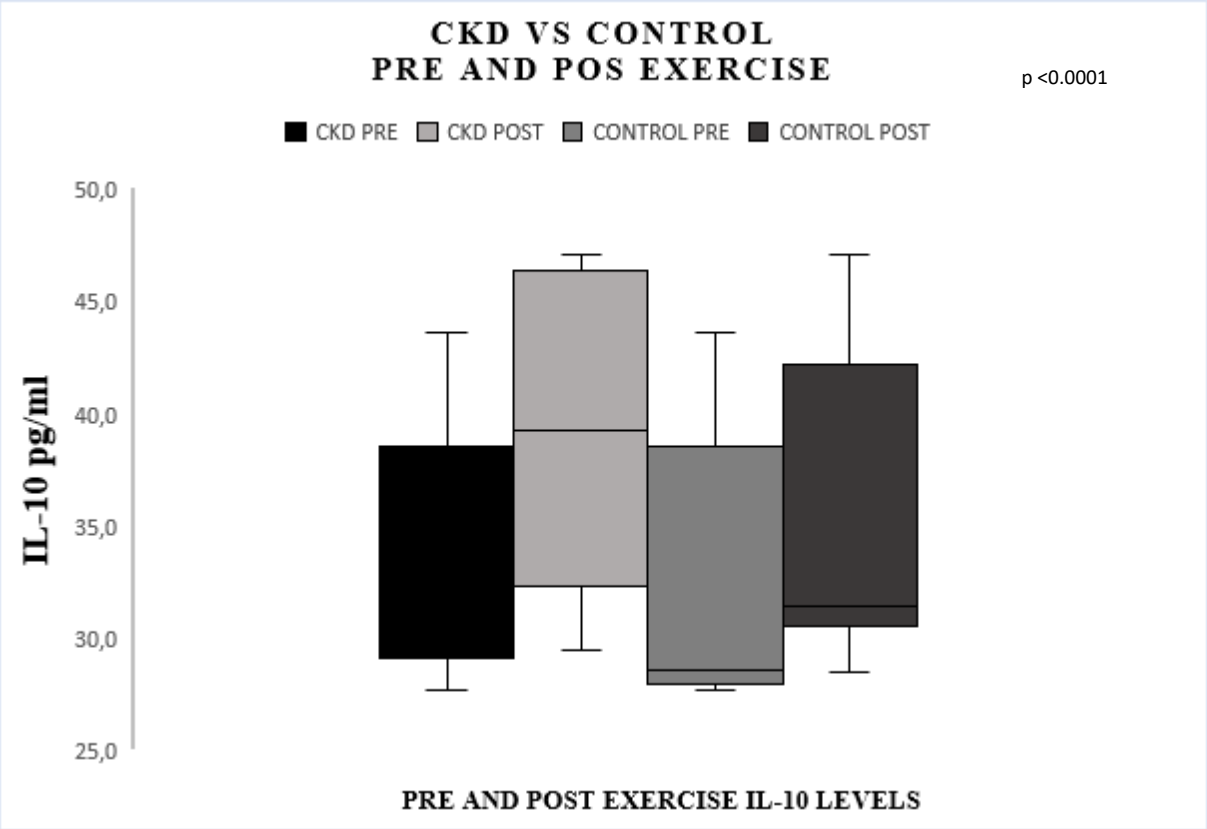
Table 2 shows the effects of an acute session of aerobic exercise on the increase in IL-10 in the CKD group and also in the control group, but IL-10 levels increased more sharply in the CKD group P <0.001.

Table 3: Correlations between inflammation and renal function biomarkers

	IL-6	**TNF-alpha**	**IL-10**	**NGAL**	**CYST-C**	**CRP**
IL-6						
r	-	**0.57***	0.3	**0.65****	**0.76****	0.4
p		***0.01***	0.2	***0.002***	***0.001***	0.07
TNF-alpha						
r	0.57*	-	**0.54***	0.4	**0.54***	0.17
p	*0.01*		***0.01***	0.08	***0.02***	0.4
Il-10						
r	0.3	0.54*	-	0.1	0.3	0.3
p	0.2	*0.01*		0.6	0.2	0.2
NGAL						
r	0.65**	0.4	0.1	-	0.83**	0.35
p	*0.002*	0.08	0.6		*0.000*	0.1

Table 3 shows a positive correlation between loss of renal function and increased levels of inflammatory markers.

Graph 1: Serum levels of IL-10 Pre and Post Exercise



ANALISYS: GENERAL LINEAR MODEL (GLM)
Graph 1 represents the acute effect of aerobic exercise on the levels of IL-10 pre and post exercise between groups. As we can see aerobic physical exercise (acute session) increased the levels of IL-10 in both groups, however there is a more pronounced increase in the group with chronic kidney disease.
ANALISYS: GENERAL LINEAR MODEL (GLM)

4 DISCUSSION

In the present study, we evaluated the effects of an acute session of aerobic exercise on markers of inflammation and biomarkers of renal function. Surprisingly, we observed an increase in serum IL-10 levels after a unique acute session of aerobic exercise.

As expected, renal function biomarkers Cystatin C and NGAL were significantly increased in patients with CKD; reflecting kidney damage caused by the pathophysiology of the main risk factors such as SAH and DM present in this population. However, we did not observe a significant change in the levels of these markers after exercise, indicating that an exercise session was not able to improve renal function in these patients. Bongers et al., 2017 (28) also did not observe the impact of resistance exercise with moderate, acute and repetitive intensity on kidney injury.

The loss of filtration renal and consequent increased of uremic toxins even in pre-dialysis stages result in inflammation state. In fact, in the present study, the CKD patients

had high levels of IL-6 and TNF-α compared to individuals without CKD and these markers correlated positively with kidney injury markers.

Unfortunately, after acute exercise, we did not observed reduction of IL-6, TNF-α, NGAL and Cystatin C levels in any of the groups studied. However, different results are reported in the literature in patients undergoing dialysis. Liao et al (29) observed that 20 minutes of intradialitic cycling, after 3 months of exercise, significantly decreased levels of IL-6 and CRP. In contrast, Dungey et al., 2015 (30) did not observe the effect of a cycle ergometer exercise for 30 min during hemodialysis on serum levels of IL-6, TNF-α or IL-1Ra and even after 6-month interdialytic aerobic exercise program. Thus, it appears that the effect of exercise on the modulation of pro-inflammatory markers is dependent on exercise time and the stage of CKD.

Surprisingly, in the present study, we observed that a single 45-minute session of aerobic exercise was able to increase the levels of anti-inflammatory cytokine IL-10 significantly in both groups (CONT and CKD), but more markedly in the CKD group; suggesting that an acute session of aerobic exercise could mitigate inflammation by inducing an increase in the anti-inflammatory cytokine IL-10. Similarly, Viana et al., 2014 (27) observed that a single 30-minute (acute) bout of walking also increased IL-10 in CKD pre dialytic patients. Dorneles et al., 2016 (31) also reported a progressive increase in IL-10 levels immediately and 30 minutes after an acute exercise session, but in obese and overweight individuals without CKD. Although our results are similar with the reports described above, we expected that an increase of IL-10 could decreased IL-6 or TNF-α or had a negative correlation between them. However, these results were not observed. In this aspect, it is worth remembering that for IL-10 to have its anti-inflammatory role; its concentration must be at least 10 - 20 times higher than pro-inflammatory cytokines (32) and it is not occurred.

A few studies analyzed the acute effects of aerobic exercise in patients with CKD. Probably, because in this population there are limitation of mobility, age and others. Therefore, this is the first report that showed increase of IL-10 after acute aerobic physical activity in CKD patients, suggesting that a single session of aerobic exercise may contribute to increase an anti-inflammatory cytokine. However, it is necessary future studies to evaluate the impact of increased IL-10 and acute aerobic exercise on outcomes in patients with CKD.

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