Sex-Specific Associations between Moderate-to-Vigorous Physical Activity and Serum MCP-1 linked to Knee Osteoarthritis Development Following ACL Reconstruction

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INTRODUCTION: Individuals who sustain an anterior cruciate ligament (ACL) injury and undergo subsequent ACL reconstruction (ACLR) are at high risk of developing knee osteoarthritis (KOA). Pro-inflammatory biochemical markers, such as monocyte chemoattractant protein-1 (MCP-1), are thought to play a key role in the onset and progression of KOA. In vitro studies suggest that physical activity (PA) may offer protective mechanisms by reducing pro-inflammatory biomarkers. However, the relationship between PA and pro-inflammatory biomarkers associated with KOA development following ACLR remains unclear. Individuals post-ACLR engage in lower levels of PA and have worse knee-related symptoms compared to their uninjured peers. In addition, females and males demonstrate sex-specific differences in PA, with research indicating that lesser moderate-to-vigorous PA (MVPA) is associated with worse cartilage composition in females, whereas greater MVPA is associated with worse cartilage composition in males. These results highlight that sex-specific analysis of KOA-related markers post-ACLR, including inflammatory biomarkers such as MCP-1, are warranted. Therefore, the objective of this study was to assess the sex-specific associations between PA and MCP-1 within the first year post-ACLR. We hypothesized that PA would be associated with serum MCP-1 in both females and males post-ACLR, but that those associations may not follow the same directionality.

METHODS: We included 28 females (age=22.3±4.6 yrs, BMI=23.5±3.0 $kg*m^{-1}$) and 20 males (age=21.9±5.3yrs, BMI=24.9±3.6 $kg*m^{-1}$) between the ages of 16 and 35 years who received primary, unilateral ACLR in this prospective, longitudinal study. All procedures were approved by the Institutional Review Board and all participants provided written consent. PA was measured at 2, 4, 6, and 12 months post-ACLR using a tri-axial accelerometer that participants wore on their right hip for 7 consecutive days (valid wear time: at least 3 weekdays and 1 weekend day for 10 hours per day). We applied Troiano cut points to determine the time participants spent in daily MVPA. Venous blood samples were collected in 5-mL serum separation tube vacutainers and subsequently batch-processed in duplicate using commercial enzyme-linked immunosorbent assays to determine the serum concentrations of MCP-1 at 6 and 12 months post-ACLR. We assessed the associations between daily MVPA at 2, 4, 6, and 12 months and serum MCP-1 at 6 and 12 months post-ACLR using Pearson's *r* correlation coefficients. In addition, independent t-tests were used to determine sex differences in age, BMI, MVPA, and serum MCP-1, and the X^2 test was used to assess differences in concomitant meniscal injury occurrence.

RESULTS: There were no differences between females and males, except that males had significantly greater MCP-1 at 6 months post-ACLR (p=0.015, Table 1). In females, greater MVPA associated with greater MCP-1. In particular, greater MVPA at 2 months was associated with greater MCP-1 at 6 (*r*=0.57, p=0.004) and 12 months (*r*=0.56, p=0.006) and greater MVPA at 6 months was associated with greater MCP-1 at 12 months (*r*=0.55, p=0.009) post-ACLR (Table 2). In contrast, males demonstrated associations between greater MVPA and lesser MCP-1, with greater MVPA at 2 and 12 months correlating with lesser MCP-1 at 6 and 12 months post-ACLR (*r* range= [-0.51, -0.57], p range= [-0.026, -0.048], Table 2).

DISCUSSION: The results of this study indicate that there are sex-specific associations between MVPA and MCP-1 within the first year post-ACLR. While greater MVPA was associated with greater inflammation in females, lesser MVPA correlated with greater inflammation in males. There is the potential that females and males may demonstrate sex-specific inflammatory physiological responses related to PA post-ACLR. However, this is speculative, since it remains unclear whether a cause-effect-relation between MVPA and inflammation post-ACLR exists or if the associations are driven by other physiological factors. Identifying the sex-specific mechanistic link between MVPA and inflammation following ACLR is important to develop adequate activity-related rehabilitation recommendations post-ACLR to mitigate joint tissue inflammation linked to KOA development.

SIGNIFICANCE/CLINICAL RELEVANCE: The sex-specific correlations between MVPA and MCP-1 highlight the need for further investigation into sex differences following ACLR to determine whether sex-specific activity modification is needed to improve long-term knee joint health post-ACLR.

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Table 1: Differences in daily MVPA and serum MCP-1 between females and males

Variable of Interest	Timepoint	Females (mean ± SD)	Males (mean ± SD)	p-value
MVPA	2 months	29.2 ± 19.2	32.6 ± 17.9	0.572
	4 months	32.3 ± 13.5	38.0 ± 15.6	0.188
	6 months	39.1 ± 23.7	49.9 ± 22.1	0.136
	12 months	40.8 ± 24.3	40.5 ± 23.5	0.959
MCP-1	6 months	125.0 ± 39.1	159.2 ± 52.6	0.015*
	12 months	129.6 ± 48.8	160.6 ± 60.4	0.067

*statistically significant difference between groups (p<0.05)

Table 2: Pearson's correlations between daily MVPA and serum MCP-1 in females and males

			MVPA							
			2 months		4 months		6 months		12 months	
	Timepoint		Females	Males	Females	Males	Females	Males	Females	Males
MCP-1	6 months	*r*	0.568	-0.571	0.033	-0.398	0.433	-0.468	0.294	-0.544
		p-value	0.004*	0.026*	0.870	0.114	0.035	0.067	0.196	0.029*
		N	24	15	27	17	24	16	21	16
	12 months	*r*	0.562	-0.536	0.120	-0.421	0.545	-0.487	0.229	-0.510
		p-value	0.006*	0.048*	0.569	0.092	0.009*	0.056	0.319	0.036*
		N	22	14	25	17	22	16	21	17