ARTICLE

Acute effect of high-intensity interval aerobic exercise on serum myokine levels and resulting tumour-suppressive effect in trained patients with advanced prostate cancer

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PURPOSE: Although skeletal muscle releases cytokines called myokines during exercise, the kinetics of the acute myokine response to exercise (exercise-induced circulatory myokine level alteration) is unknown in patients with advanced prostate cancer. We measured myokine levels in serum obtained from patients with metastatic castrate-resistant prostate cancer (mCRPC) before and after exercise and assessed the growth-suppressive effect of the serum by applying it to a PCa cell line.

METHODS: Nine patients with mCRPC (age = 67.8 ± 10.1 years, time since mCRPC diagnosis 36.2 ± 22.5 months) undertook 34 min of a high-intensity interval exercise session on a cycle ergometer. Blood was collected immediately pre, post and 30 min post. Serum levels of secreted protein acidic and rich in cysteine (SPARC), oncostatin M (OSM), interleukin-6 (IL-6), interleukin-15 (IL-15), decorin, irisin, and IGF-1 were determined. Growth of the androgen-independent PCa cell line DU-145 exposed to serum collected at three points was measured.

RESULTS: There was a significant elevation of SPARC (19.9%, $P = 0.048$), OSM (11.5%, $P = 0.001$), IL-6 (10.2%, $P = 0.02$) and IL-15 (7.8%, $P = 0.023$) in serum collected immediately after exercise compared to baseline, returning to baseline after 30 min rest. A significant reduction in DU-145 Cell growth and the Cell Index area under the curve at 72 h incubation was observed with the presence of serum obtained immediately post-exercise (Cell Index at 72 h: 16.9%, $P < 0.001$; area under the curve: 15.2%, $P < 0.001$) and with the presence of serum obtained 30 min post-exercise compared to baseline (Cell Index at 72 h: 6.5%; area under the curve: 8.8%, $P < 0.001$).

CONCLUSION: This study provides preliminary evidence for an acute exercise-induced myokine response and tumour growth suppression in serum after a bout of high-intensity interval exercise in patients with advanced PCa.

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INTRODUCTION

Exercise oncology, the application of exercise medicine to cancer care, is now recognised in clinical oncology [1]. Findings from clinical trials confirm the efficacy of exercise for improving a range of health outcomes, including body composition, physical function, muscular strength, aerobic capacity, psychological factors, and quality of life, for patients with prostate cancer (PCa) [2–4]. Further, an association between increased volume and intensity of physical activity and reduced cancer-related mortality [5] and disease progression [6] has been reported in observational studies, providing a strong case for all patients with PCa to engage in exercise.

Exercise is known to induce numerous acute physiologic responses, including alteration of blood contents, with the elevation of exercise-induced secretory factors in blood in response to exercise suggested as having a tumour-suppressive role [7–11]. For example, serum obtained from patients with breast cancer or colon cancer immediately after an acute bout of exercise applied to breast cancer cell lines or colon cancer cell lines reduced viability compared to the application of serum obtained before the exercise bout [8, 9]. Importantly, serum collected from 10 healthy individuals after a single bout of continuous cycling exercise significantly reduced the proliferation of the PCa cell line LNCaP by 31% [11]. Alterations of circulatory levels of epidermal growth factor (EGF), epinephrine, norepinephrine, interleukin-6 (IL-6), tumour necrosis factor-α, and interleukin-8 (IL-8), were also reported in these studies after an acute bout of exercise [8, 9, 11], suggesting a tumour suppressive

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role of exercise could occur altering the concentration of such signalling molecules in the blood.

Recently, skeletal muscle has been identified as having a substantial endocrine function through the synthesis and secretion of cytokines (termed myokines) into the circulation with consequent health benefits [12, 13]. Preclinical studies have also demonstrated a tumour-suppressive role of these myokines after applying them directly to various PCa cell lines in culture [14]. For instance, reduced proliferation of PCa cell lines LNCaP, DU-145, and PC-3 were reported after the application of secreted protein acidic and rich in cysteine (SPARC) [15], irisin [16] and decorin [17]. Further, oncostatin M (OSM) and interleukin 15 (IL-15), can also limit the growth of cancer cells by altering the tumour microenvironment [14].

Despite preclinical evidence demonstrating a tumour-suppressive role of myokines and substantial involvement of skeletal muscle during exercise [14], there is a limited understanding of the endocrine role of skeletal muscle on tumour-suppression in patients with PCa due to a paucity of research data. Furthermore, given that the only previous evidence of PCa suppression was obtained from healthy individuals [11], it is important to examine the contribution of exercise to a systemic anti-tumour environment in patients with different PCa stages to enhance our understanding of targeted exercise medicine. Especially, patients with mCRPC frequently receive ongoing treatment with androgen receptor-targeted agents (ARTA), which significantly compromise muscle tissue and may impact its endocrine capacity [18–20]. We recently reported that 6 months of aerobic plus resistance training at high intensity in patients with mCRPC undertaking androgen suppression results in an elevation of serum myokine concentrations at rest and exhibits growth suppression in DU145 cells [21]. However, it needs to be established whether these patients can mount an acute exercise response above and beyond the elevated resting levels of myokines resulting from their chronic training. Therefore, we examined myokine levels in the serum collected before and after a single bout of high-intensity interval aerobic exercise in trained patients with mCRPC undertaking anti-androgen therapy and the tumour-suppressive effect of the collected serum.

MATERIALS/SUBJECTS AND METHODS

Participants

Based on the Cell Index result from our previous report (Pre: 5.829 ± 1.112, Post: 4.566 ± 1.1515) [22], 7 participants are required to achieve 0.80 power at an α level of $p < 0.05$ for a two-tailed comparison. As such, we aimed to recruit 10 patients, however, only 9 patients with mCRPC were eventually recruited from the INTERVAL-GAP4 trial (Clinical Trials Registry: NCT02730338) [23] at the Exercise Medicine Research Institute (Edith Cowan University, WA, Australia) and took part in this study. mCRPC was defined as adenocarcinoma of the prostate with the progression of systemic metastatic disease despite castrate levels of testosterone (<50 ng/dl) obtained either via orchiectomy or undergoing androgen deprivation therapy (ADT) with a gonadotropin-releasing hormone agonist or antagonist [23]. Patients enrolled in this study had been allocated to the exercise group of the INTERVAL-GAP4 trial and had completed at least the first 12 weeks of the exercise intervention (including 4 weeks of familiarisation). The study was funded by the Movember Foundation and ethically approved by the Human Research Ethics Committee at Edith Cowan University (ID: 13236 NEWTON). Written informed consent was provided by all eligible patients before participation.

A single bout of high-intensity interval aerobic exercise

Patients were asked to complete two high-intensity interval aerobic exercise sessions. A familiarisation session was undertaken one week before the actual test session during their usual supervised, in-clinic aerobic exercise session for the INTERVAL-GAP4 trial [23]. These exercise sessions were similar but slightly modified from the usual supervised aerobic exercise program prescribed for INTERVAL-GAP4 [23]. Specifically, the exercise session consisted of a 5 min warm-up at an intensity of 50–60% of maximum heart rate determined at the most recent VO_2max test or an intensity of 5–6 on the 0–10 Borg scale rating of perceived exertion (RPE). This was followed by 6 sets of 4 min of high-intensity cycling at an intensity of 70–85% of maximum heart rate (7–8 RPE) with 2 min active recoveries at 50–65% of maximum heart rate (5–6 RPE) between the high-intensity bouts, ending with a 5 min cool-down (Fig. 1). Excluding the warm-up and cool-down, the total exercise duration (high-intensity bouts + active recovery bouts) was 34 min. Heart rate was recorded using a chest strap monitor (T31-Coded Transmitter and FT1 Heart Rate Monitor, Polar Electro, Australia) every 2 min of the high-intensity bouts and every 1 min of the low-intensity bouts with RPE collected at the same time points.

Blood assessment and analysis

On the day of testing, patients were asked to abstain from food or drink except water for 2 h before commencing. Blood was collected immediately before (baseline), immediately after (post), and 30 min after exercise cessation (post 30 min). Approximately 8 ml of blood was collected at each time point using a serum separating tube. Serum was extracted from collected blood samples and stored at −80 °C until further analysis. Serum levels of SPARC (ab220654, Human SPARC ELISA Kit, Abcam, Cambridge, UK), oncostatin M (OSM; ab215543, Human Oncostatin M/OSM ELISA Kit, Abcam, Cambridge, UK), IL-6 (ab178013, Human IL-6 ELISA Kit, Abcam, Cambridge, UK), IL-15 (ab218266, Human IL-15 ELISA Kit, Abcam, Cambridge, UK), decorin (ab99998, Human Decorin ELISA Kit, Abcam, Cambridge, UK), irisin (CSB-EQ027943, Human Irisin ELISA Kit, Cusabio, Chain), and IGF-1 (ab211651, Human IGF1 SimpleStep ELISA Kit, Abcam, Cambridge, UK) were analysed using commercially available enzyme-linked immunosorbent assay (ELISA) kits.

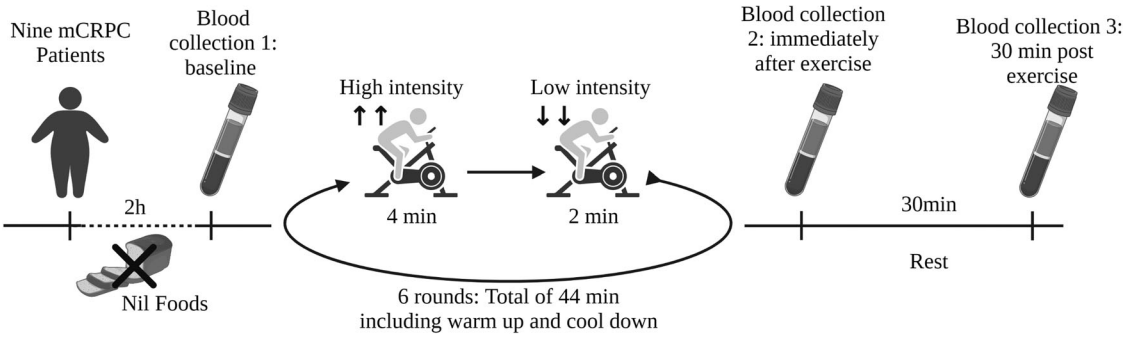

Fig. 1 Exercise and blood sample timing. Blood was drawn immediately before 44 minutes of high intensity interval training, immediately post and 30 minutes post exercise.

Real-time cellular analysis

The human PCa cell line, DU-145, was obtained from The Harry Perkins Institute, Nedlands, WA, Australia, originally purchased from American Type Culture Collection (ATCC HTB-81). Cells were cultured in RPMI-1640 media containing 10% foetal bovine serum and routinely passaged at ~80% confluence. The growth of DU-145 cells was assessed using a Real-Time Cellular Analysis (RTCA) system, xCELLigence DP unit and E-plate (ACEA Bioscience, CA, USA) in the presence of collected human serum from each patient at three different collection time points (pre/post/30 min-post exercise). The Individual well of the E-plate was seeded with 15,000 DU-145 cells with 100 µl of serum-free RPMI-1640. After 24 h of starvation, 100 µl of growth media (RPMI-1640) containing 20% human serum from each patient and time point (final concentration of 10%) was added to the individual well of the E-plate. The growth of DU145 cells with the presence of collected individual serum was examined in duplicate. The plates were incubated for 72 h and growth was recorded in the unit of Cell Index every hour. Cell Index is a unit used to indicate the number of adhered cells on the bottom of the plate, recording the time electric current travels through the well plate.

Table 1. Patient characteristics.

	Mean ± SD
Patient characteristics	
Age (years)	67.8 ± 10.1
Time since diagnosis of mCRPC (months)	36.3 ± 22.5
Weight (kg)	94.9 ± 22.6
Total Lean Mass (kg)	60.7 ± 13.7
Lean Mass Percent (%)	64.1 ± 2.6
Lean Mass Index (kg/m^2)	18.6 ± 2.4
Total Fat Mass (kg)	34.5 ± 8.9
Fat Mass Percent (%)	36.3 ± 2.6
Body Mass Index (kg/m^2)	30.4 ± 4.5
Pre-exercise assessment for intensity adjustment	
Absolute VO_2max (L/min)	2.43 ± 0.92
Relative VO_2max (ml/kg/min)	24.1 ± 5.8
Maximum Heart Rate (beat/min)	159 ± 11

VO_2max maximum oxygen consumption.

Statistical analysis

Data were analysed using R software (v4.0.2, The R Foundation), with the geepack package (v1.3-2, Halekoh, 2006) for statistics, ggplot2 package (v3.3.3, Wickham, 2020) for visualisation and Desctools package (v0.99.41, Signorell, 2021) for the area under the curve (AUC) calculations. Generalised estimating equation (GEE) linear regression models were used to analyse differences between repeated time points (three-time points, baseline/post/30 min-post exercise) among the patients at each incubation hour. Serum myokine level and Cell Index AUC values are presented in a graph with median and interquartile range (IQR). The Cell Index values are presented in a graph with mean and standard error (SE). Tests were two-tailed, and significance was set at $P < 0.05$.

RESULTS

Patient characteristics and exercise intensity

Patient characteristics are summarised in Table 1. The mean age of the nine patients was 67.8 ± 10.1 years. Three patients had bone metastases, 1 had nodal metastases, and 5 had bone and nodal metastases. The mean relative VO_2max was 24.1 ± 5.8 ml/kg/min (absolute VO_2max; 2.43 ± 0.92 L/m), with a maximum heart rate of 159 ± 11 beats per minute. To evaluate the exercise session, the plotted graph of indicators for the exercise intensity (percent heart rate [objective measure]; RPE [subjective measure]) are shown in Fig. 2. The two indicators showed similar patterns for each high- and low-intensity bout, indicating that exercise intensity was appropriate.

Serum myokine levels

Serum myokine levels at the three different time points (baseline/post/30 min post) are shown in Fig. 3. There was a significant difference in repeated time points for SPARC ($P = 0.002$), OSM ($P = 0.015$), IL-6 ($P = 0.045$), and IL-15 ($P = 0.023$), as well as a borderline trend for decorin ($P = 0.085$). Post-analysis showed significant elevation of SPARC (19.9%, $P = 0.048$), OSM (11.5%, $P = 0.001$), IL-6 (10.2%, $P = 0.02$), and IL-15 (7.8%, $P = 0.023$) in serum collected immediately after exercise compared to serum collected at baseline with no difference between post 30 min and baseline (Fig. 3).

Real-time cellular analysis

The Cell Index was recorded every hour for 72 h, and the time-course changes in Cell Index are presented in Fig. 4A. A GEE model was used to examine the difference in the Cell Index of DU-145 every 6 h of cell incubation between the wells with the presence of serum collected from individual patients at three different

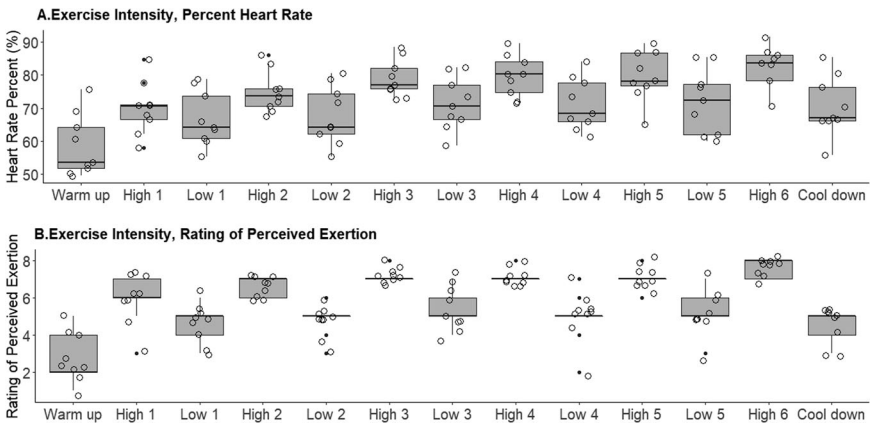

Fig. 2 Exercise intensity changes during high-intensity interval aerobic exercise. A Percent heart rate during the exercise session. **B** Rating of perceived exertion during the exercise session. The *x*-axis indicates the individual bouts of exercise with altered exercise intensity such that High 1 indicates the first high-intensity bout, Low 1 indicates the first low-intensity recovery bout, High 2 the second high-intensity bout, etc. The circles indicate individual data, with a box-and-whisker representations of the whole group (median, IQR).

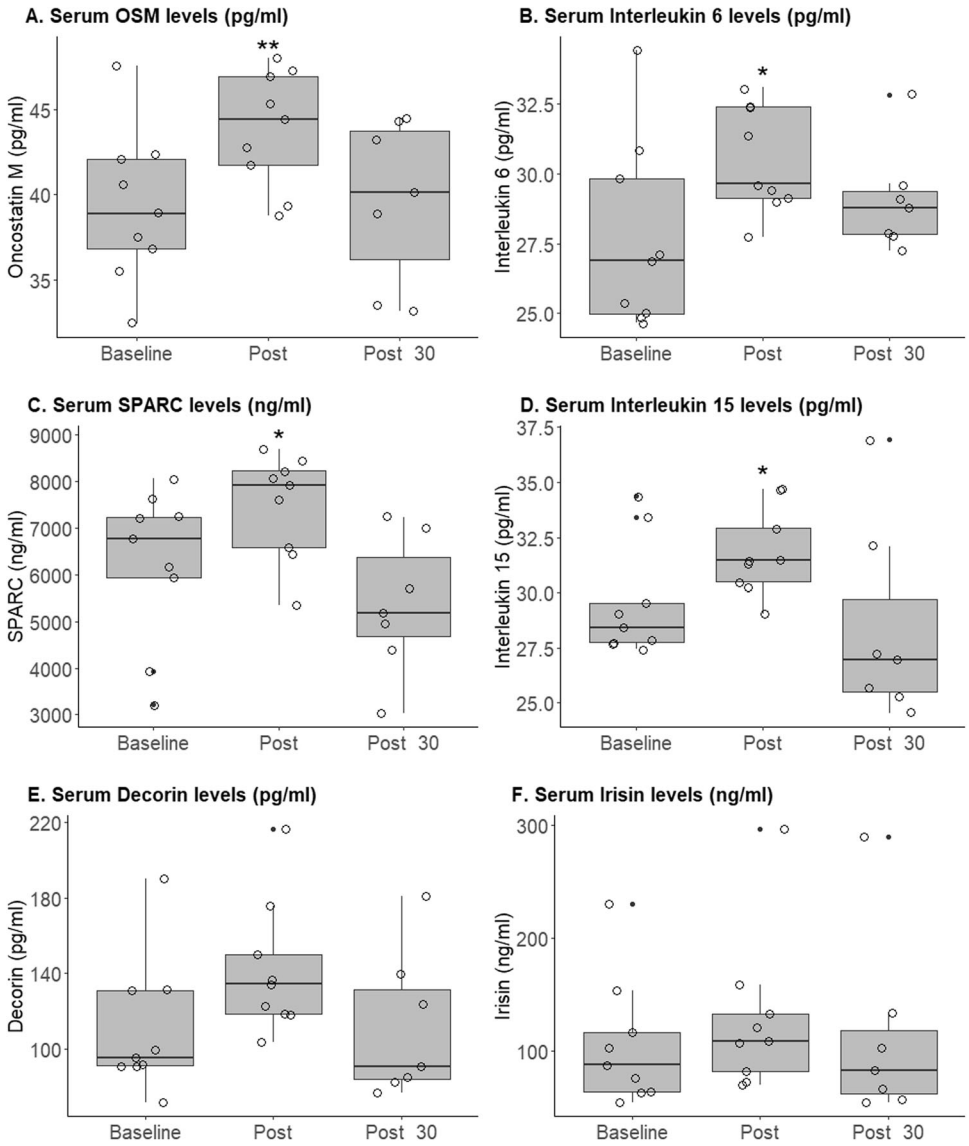

Fig. 3 Serum myokine levels. Serum myokine levels at repeated time points (baseline, immediately post, and 30 min post-exercise). **A** Oncostatin M, (**B**) IL-6, (**C**) SPARC, (**D**) IL-15, (**E**) Decorin, (**F**) Irisin. The circles indicate individual values with box-and whisker representation of the whole group (median, IQR). *$P < 0.05$, **$P < 0.01$ compared to baseline.

collection time points (pre/post/30 min-post exercise). In addition, the AUC of the Cell Index was calculated for different incubation times (Fig. 4B, 0–≤24 h; Fig. 4C, 0–≤48 h; Fig. 4D, 0–≤72 h) for the three different collection time points (pre/post/30 min-post exercise) and a significant difference was evident in mean AUC ($P < 0.01$). Post-analysis revealed a significant reduction in 0–24 incubation hours AUC with serum obtained 30 min after exercise cessation compared to serum obtained before the exercise session (4.91%, $P < 0.001$) (Fig. 4B). A significant reduction was also observed in AUC for 0–48 and 0–72 incubation hours with the presence of serum collected immediately after exercise (0–48, 9.67%, $P < 0.001$; 0–72, 16.93%, $P < 0.001$) and 30 min after exercise cessation (0–48, 6.91%, $P < 0.001$; 0–72, 8.82%, $P < 0.001$) compared to serum obtained at baseline.

DISCUSSION

This study aimed to examine whether a single acute bout of exercise elevates skeletal muscle-secreted cytokines called myokines in patients with mCRPC undergoing anti-androgen therapy who had completed 12 weeks of exercise within the INTERVAL-GAP4 intervention. We demonstrated that high-intensity interval aerobic exercise significantly elevates serum myokines OSM, IL-6, SPARC, and IL-15 with a borderline increase of decorin in these patients. Furthermore, we demonstrated reduced growth of the castrate resistance PCa cell line DU-145 in the presence of serum collected after high-intensity aerobic exercise compared to serum obtained before exercise.

This study is the first to examine myokine expression in serum before and after a single exercise session in patients with mCRPC on anti-androgen therapy. Despite the substantial activation of skeletal muscle during exercise, there has been limited research investigating the potential tumour suppressive role of skeletal muscle-secreted molecules. Previously, multiple exercise trials with a single acute bout of exercise have demonstrated elevation of various myokines, such as IL-6 [24–26], OSM [27], SPARC [28], IL-15 [29–31], decorin [32, 33] and irisin [34, 35] in non-cancer populations, and the role of myokines in providing health benefits [12, 13]. There are significant differences in muscle and fat mass as well as metabolic and physiological differences between cancer

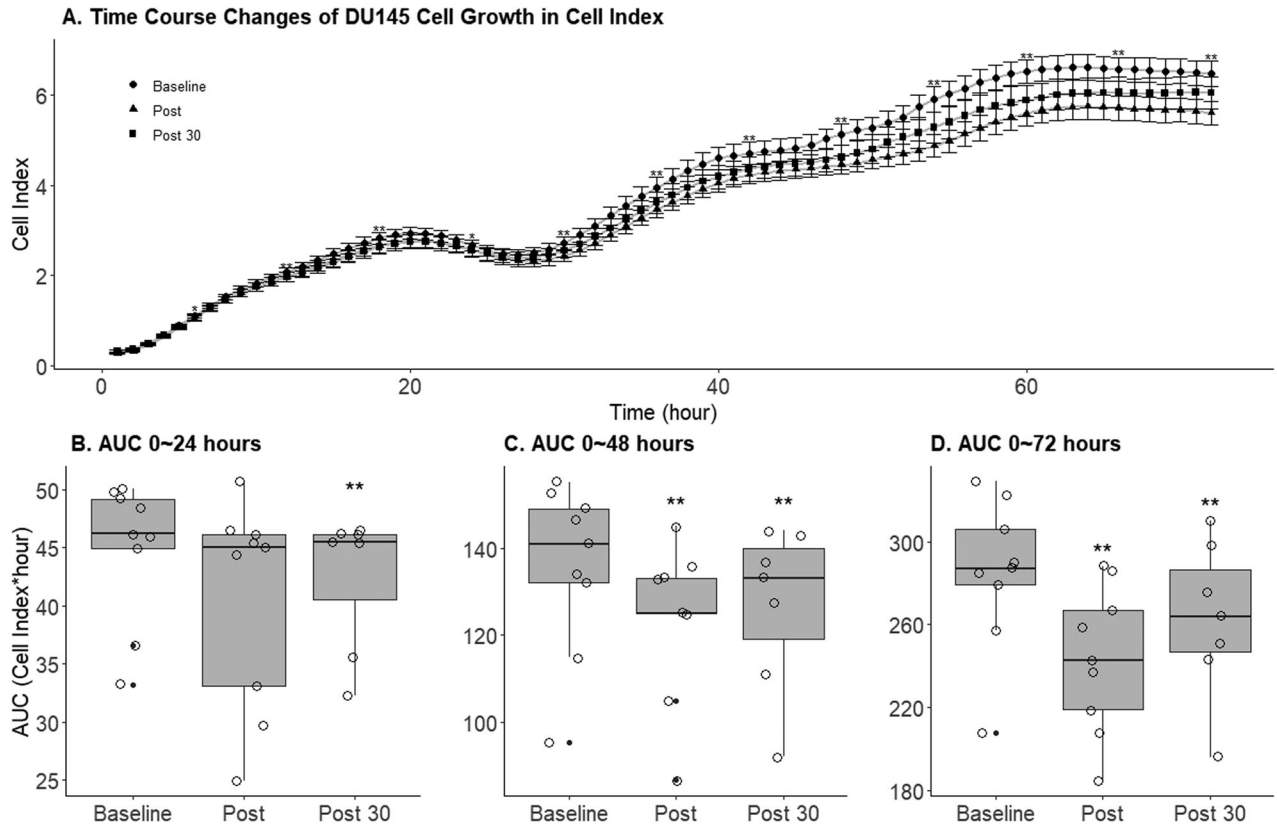

Fig. 4 Real-time cell growth analysis. DU-145 cells were starved for 24 h, and growth media containing 10% serum from repeated time points was applied at incubation time 0 h. **A** Time-course of DU-145 Cell Index after application of serum acquired from mCRPC patients at repeated time points (baseline/post exercise/post-30 min exercise) (Mean ± SE). Significance is reported every 6 h of incubation. **B** The calculated AUC for repeated time points between 0 and 24 h. **C** The calculated AUC for repeated time points between 0 and 48 h. **D** The calculated AUC for repeated time points between 0 and 72 h. The circles indicate individual data, with box-and-whisker representations of the whole group (median, IQR). $^{*}P < 0.05$, $^{**}P < 0.001$ compared to baseline.

patients and the non-cancer population as a result of both the underlying disease and its treatments. As such, it was important to examine if exercise-related myokine responses (exercise-induced circulatory myokine level alteration) are observed after exercise in patients with mCRPC given the impact of disease and treatment on muscle mass and quality [14] as well as exercise capacity [36].

In the current study, a significant elevation of OSM, IL-6, SPARC, and IL-15 in the serum collected immediately after exercise was observed compared to serum collected at baseline. Moreover, elevated serum OSM, IL-6, SPARC, and IL-15 levels immediately after exercise returned to baseline levels after 30 min of resting, indicating patients with a high disease load and undertaking androgen suppression for mCRPC can elicit acute exercise responses regarding myokine expression similar to the non-cancer population. These observations are particularly important as there has been no research investigating the kinetics of myokine response in patients with mCRPC, with only speculation regarding the myokine response inferred from previous research [14]. Although this study was not conducted in a large number of patients, the rigorous exclusion and inclusion criteria of the INTERVAL-GAP4 trial [23] and for the current sub-study allow us to demonstrate the alteration of myokines in a specific patient group. Further, not only to examine the tumour suppressive effect of a single bout of exercise, we recruited the patients who completed 3 months of exercise intervention as part of the INTERVAL-GAP4 trial [23] to evaluate whether a bout of exercise could illicit additional tumour suppressive effects to the anti-tumour environment that was established by chronic exercise training. As such, this study confirmed an acute myokine response in exercise-trained patients with mCRPC undertaking androgen suppression despite the structural, metabolic and physiologic alterations observed in the patients [18].

Our previous studies demonstrated a significant growth reduction of the PCa cell line DU145 with serum obtained after chronic exercise training in patients with localised PCa [22] and advanced PCa [21]. However, investigation into the effect of a single bout of exercise is required to enhance our understanding of exercise dose effects and subsequent prescription of exercise. In a previous comprehensive review [14] on myokines and the potential exercise-induced tumour suppressive mechanisms, it was suggested that at least 30 min of moderate-intensity continuous or high-intensity interval aerobic exercise is required for a subsequent myokine response in these patients. We provided an exercise program with similar volume and intensity for this study [14] and confirmed that this volume and intensity is sufficient to elicit a myokine response in patients with mCRPC.

The tumour suppressive role of exercise-conditioned serum after a single bout of exercise has been demonstrated in various cancer cell lines [8–11]. Importantly, Rundqvist et al. [11] and Hwang et al. [10] showed a growth-suppressive effect of serum obtained after a single bout of aerobic exercise compared to unexercised serum in a PCa cell line (LNCaP and PC-3), with significant alteration of serum levels of EGF, IGFBP-1, OSM, and SPARC. However, the serum was obtained from healthy young adults, limiting clinical relevance. As such, we have obtained and applied the serum from patients with mCRPC [22] to PCa cell lines to better evaluate clinical relevance. We also selected a single cell line representing the characteristic of mCRPC, DU-145 (androgen-

insensitive, metastatic capacity) to further increase the clinical relevance of our study [21]. As such, our observation of a significant reduction of DU-145 Cell Index with the presence of serum obtained immediately after a single exercise bout compared to baseline, provides a clinically relevant insight compared to previous studies.

The current study has some limitations that should be noted. This study was not designed to investigate the threshold intensities and volumes for myokine response in patients with mCRPC. In addition, we only implemented high-intensity interval aerobic training and, as such, we are unable to compare the myokine response to different exercise modes (e.g. resistance vs. aerobic exercise). Moreover, although we reported a significant alteration of the myokine responses and growth suppression of a PCa cell line after administrating serum from patients, the current study did not include in-depth intercellular mechanistic measures to investigate potential signal pathways. Lastly, as the present study could not differentiate the effect of other physiological changes in the circulatory system (e.g. altered metabolism, lower glucose, lactic acid), further study is required to fully understand the effect of exercise on tumour suppression. As such, potentially employing antibody-based methods to serially remove individual myokines from the conditioned serum could help identify the effect of myokines influencing tumour biology.

In conclusion, serum myokine concentrations are elevated after a single bout of high-intensity interval aerobic exercise and there is a tumour suppressive effect of acute exercise-conditioned serum in exercise-trained patients with mCRPC. We have previously demonstrated that chronic exercise training shifts resting myokine levels upward, providing a more anti-cancer systemic environment and these latest findings are that an acute bout of exercise results in a further increase in myokine concentration, albeit transient. Pragmatically, this suggests patients with mCRPC should exercise chronically to elevate resting myokine levels, and also complete acute bouts of exercise regularly to further "dose" their system. However, additional research is required to investigate threshold exercise intensity, volume, and optimal exercise mode to enhance our understanding of the appropriate modes and exercise dosages for patients with mCRPC regarding myokine expression. In addition, an investigation of the effect of myokine alterations on the intercellular signalling pathways is required to further identify potential additive or synergic interaction of exercise-induced myokines with PCa treatments.

DATA AVAILABILITY

The data are available for bona fide researchers who request it from the authors.

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AUTHOR CONTRIBUTIONS

J-SK and RU Newton had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. J-SK, RUN, DRT and DAG conceptualised the study. J-SK and RUN designed the study. RUN, J-SK, DAG and NHH collected the clinical information, body composition and fasting blood samples. NHH and SAK supervised and directed the overall study's implementation, data collection, and data monitoring. J-SK analysed the data. J-SK and RUN were responsible for the drafting of the paper. RUN, DRT, DAG, TDC, ADR, EG, CJC, SAK and FS provided administrative, technical, intellectual and material support. J-SK, RUN, DRT, DAG, TC, ADR, NHH, ESG, CJR, SAK and FS reviewed and edited the paper prior to submission.

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COMPETING INTERESTS

The authors declare no competing interests. Sponsors had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the paper; and the decision to submit the paper for publication.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Edith Cowan University Human Research Ethics Committee (ID: 13236 NEWTON). Informed consent was obtained from all subjects involved in the study prior to inclusion.

ADDITIONAL INFORMATION

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