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Blood monitoring in the English Premier League: Effect of curcumin supplementation on blood biomarkers of recovery

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A B S T R A C T

Reducing inflammation during periods of frequent match play may be an important objective to promote player recovery and protect player health. The authors aimed to investigate the effect of curcumin supplementation on biomarkers of recovery in response to weekly match play during an English Premier League (EPL) season. We conducted a longitudinal analysis of 18 EPL games during the 2019 – 2020 season (n = 22), and used an interrupted time-series design to analyse the effect of curcumin supplementation on biomarkers of inflammation and pro-oxidant status. Participants consumed 2 × 500 mg capsules (Elite Opti-Turmeric, Healthspan, Ltd) for a total dose of 1000 mg of curcumin (as recommended by the manufacturer), the morning of game day -2 (GD-2), game day -1 (GD-1) and immediately post-game during each supplementation period. Relationships between biomarkers and co-variates were examined using linear mixed effects models. No significant effect was found for the intervention on C-reactive protein (CRP) responses. No significant relationships were observed for all other explanatory variables on CRP responses. We found a significant association between hydroperoxides (HPX) responses and time (0.005 mmol/L H_2O_2; $p = 0.020$). No significant effect was found for the intervention on HPX responses. No significant relationships were observed for all other explanatory variables and HPX. We report that curcumin ingestion at the dose and protocol prescribed is not effective, at least at a group level, for attenuating biomarker responses within the applied setting of professional soccer.

1. Introduction

Soccer match play is characterized by many high intensity episodes of physical stress, inducing skeletal muscle fibre damage, and predisposing players to recurrent episodes of acute inflammation (Ispirlidis et al., 2008). Acute inflammation is a vital protective process, acting to clear damaged tissue and promote repair, however, overwhelming inflammation can result in secondary damage and promote maladaptive tissue remodelling (Markworth et al., 2016). During periods of frequent match play,

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the recovery between successive games may not be adequate for the restoration of normal homeostasis and the resolution of the inflammatory response (Mohr et al., 2016), potentially leading to the development of chronic low-grade inflammation. Reducing inflammation during periods of frequent match play may therefore be an important objective for sports science and medicine staff in order to protect player health and recovery. Long-term supplementation with anti-inflammatory compounds is not recommended (Owens et al., 2019). However, when adaptation is inconsequential, for instance, during periods of heavy workload whilst 'in-season', or during periods of fixture congestion when the ability to recover in sufficient time is compromised, nutritional supplementation may be beneficial in aiding the timely recovery of the player. Furthermore, if we know that an inflammatory episode/insult will occur by virtue of competition, pre-competition acceleration of inflammation resolution via targeted nutritional supplementation may represent a practical approach for preventing the development of low-grade inflammation and promoting the timely recovery of the elite soccer player in-season.

Curcumin is a component of the spice turmeric and is often used to reduce exercise-induced inflammation (Heaton et al., 2017) due to its potential antioxidant and anti-inflammatory properties (Fernández-Lázaro et al., 2020). Moreover, positive effects on inflammatory markers have been observed when consumed prior to exercise in physically active individuals (McFarlin et al., 2016; Szymanksi et al., 2018; Tanabe et al., 2019). However, data in elite athletes are generally absent from the literature, with only one study conducted to date (Delecroix et al., 2017). Delecroix et al. (2017) observed that curcumin supplementation taken before and after exercise attenuated some (i.e., reduction in sprint mean power output was moderately lower in the experimental condition), but not all aspects of muscle damage, in a group of elite rugby players. Heaton et al. (2017) suggest that supplementation with oral curcumin may be beneficial for athletes participating in high-intensity exercise with a significant eccentric load, and its utility warrants investigation in elite soccer players. To the knowledge of the authors, research investigating the efficacy of an anti-oxidant/anti-inflammatory intervention in the English Premier League (EPL) are absent from the literature. Therefore, this study was designed to investigate the efficacy of curcumin supplementation on biomarkers of recovery during an EPL season. We hypothesized that biomarker responses could be altered by accelerating the resolution of inflammation using curcumin supplementation prior to competition.

2. Methods

2.1. Participants

Twenty-two players (age = 25 years, *SD* = 3 years, height = 182 cm, *SD* = 8 cm, weight = 75 kg, *SD* = 6 kg, body mass index (BMI) = 23, *SD* = 2) were recruited to participate from the first team of an EPL club. Ethical approval was obtained from the University of Galway research ethics committee and written informed consent was provided by all participants.

2.2. Design overview

We conducted a longitudinal analysis of 18 English FA Premier League games during the 2019 – 2020 season. We used an interrupted time-series design to analyse the effect of curcumin supplementation on biomarkers of recovery. Following a seven-game control period (i.e., Control 1; August/September), participants completed a four-game supplementation block (i.e., Case 1; September/October), followed by a second control period of two games (i.e., Control 2; November) and another supplementation block of five games (i.e., Case 2; November/December).

Training was prescribed by coaching staff and was deliberately not influenced by the study design or the research personnel. The athletes training load varied in intensity and volume depending on factors including but not limited to the following: player status (starter/bench player), time of season, upcoming games, injuries and illnesses. Match load data (volume, intensity, minutes) were collected and recorded for each game. As appropriate, players were classified as injured and ill by the medical staff. Only fit, healthy and training players were included in the experimental trial.

2.3. Blood biomarkers

Blood biomarker data were collected twice weekly (pre- and post-game) at the same time of day and included the following: high sensitivity C-Reactive Protein (CRP) and plasma hydroperoxides (HPX) via point-of-care blood tests. Over the course of the first half of the competitive season (August to December), repeated measurements of CRP and HPX were taken from these players before and after each of 18 games. Testing was carried out between 9 AM and 11 AM, with pre-game measurements taken on game day -1 (GD-1). The timing of the post-game measurements were dependent on the schedule prescribed by the coaching staff, and were taken on either game day +1 (GD+1), game day +2 (GD+2), game day +3 (GD+3), game day +4 (GD+4) or a combination thereof. Players were asked to report for testing in a fasted and hydrated state, where players reported not being fasted, this was noted and factored into the analysis. Inflammation was immediately measured with an immunoturbidimetric high sensitivity CRP assay (Cube-S point of care analyzer; Eurolyser Diagnostica GmbH, Salzburg, Austria) using a 20 uL ethylenediaminetetraacetic acid capillary tube. This photometric measurement of CRP is based on an antigen-antibody reaction between antibodies to human C-reactive protein bound to polystyrene particles and C-reactive protein present in the sample. All the biochemistry is contained within the test cartridges supplied by the manufacturer. The manufacturer reports a coefficient of variation for the assay of 2.8% for whole blood with a correlation coefficient R^2 of 0.951 against a clinical laboratory gold standard. The measurement range of the analyzer is 0.5 – 20.0 mg/L.

Pro-oxidant status was determined by measuring biological footprints of oxidative damage downstream of the site of reactive oxygen species production, using the Free Oxygen Radical Test calorimetric assay, an indirect measure of reactive intermediary by products of in vivo lipid, protein, and nucleic acid oxidation (plasma hydroperoxides). Whole-blood capillary samples (20 uL for FORT) were taken from the earlobe in heparinized capillary tubes. These were mixed immediately with reagent, centrifuged at 5000 r·min^{-1} (2000 g) for 1 min, and analyzed according to the manufacturer's instructions, using a Callegari analyzer (Callegari SpA, Catellani Group, Parma, Italy) at 37 °C, with absorbance set at a wavelength of 505 nm for the calculation of FORT. Lewis et al. (2016) previously published in detail the methodology for the FORT assay. The manufacturer of the assays reports a coefficient of variation < 5% for FORT, and Lewis et al. (2016) have reported a coefficient of variation of 3.9%.

2.4. Match load assessment

Games were analysed during the 2019 – 2020 season, using a multi-camera computerised tracking system (Second Spectrum Inc, CA, USA). Game minutes, total distance and high intensity running distance (defined as distance covered at > 21 km/h) were recorded each game via cameras positioned in each of the stadiums and were analysed using match-analysis software (Second Spectrum Inc, CA, USA) to produce a single data set of each player's activity during a match.

2.5. Dietary supplementation

The dosing strategy selected (i.e., the timing, length and dose) was based upon a number of factors, including previous research (McFarlin et al., 2016; Szymanksi et al., 2018; Tanabe et al., 2019), the manufacturer recommendations and considerations regarding player compliance. Supplementation was initiated two days prior to each game. Participants consumed 2 × 500 mg capsules (Elite Opti-Turmeric, Healthspan, Ltd) for a total daily dose of 1000 mg of curcumin (as recommended by the manufacturer), the morning of game day -2 (GD-2), game day -1 (GD-1) and immediately post-game during each supplementation period. Each capsule contained: NovaSOL® curcumin 500 mg), vitamin C (20 mg). Participants maintained their habitual diet routine throughout each supplementation period. Supplement adherence was monitored via verbal confirmation by the same research personnel. To ensure compliance, the supplement was given only during the supplementation block, and on the days specified (GD-2, GD-1, Game Day). Where players reported non-compliance, this was noted and factored into the analysis. Subject non-compliance was broadly defined as subjects that did not adhere to the study protocol (i.e., missed supplement doses, missed testing appointments).

2.6. Statistical analysis

Summary statistics were calculated for each response variable and for the high intensity running covariate by testing time (Pre-/Post-) and stage (Control or Case). The stage variable was coded as a factor (with 4 levels) to account for the interrupted time series study design used (i.e., control / case / control / case). Linear mixed models were used to estimate the effect of the intervention on each response variable while controlling for stage, testing time, the number of days post-game where the post measurement was taken (i.e., GD+1, GD+2, GD+3, GD+4) and the amount of high intensity running recorded in the game in question. In order to account for the hierarchical structure in the design random effects were included for players, games and stage in order to account for the correlation within players over time, and for players within games and stages. The analysis excluded goalkeepers. Candidate models that were considered a-priori included models with an interaction term to adjust for potential differences in the mean response at the pre-testing time in each stage, models that included distance as an additional covariate and models using the gamma distribution to account for the strictly positive responses. All analyses were performed with the use of R (www.r-project.org, a language and environment for statistical computing software). A p value of less than 0.05 was considered to indicate statistical significance.

3. Results

A total of 22 athletes completed the study. Summary statistics for HPX and CRP responses by stage are detailed in Table 1. The effect of explanatory variables on CRP responses are detailed in Table 2. No significant effect was found for the intervention on CRP responses (Figure 1A). No significant effects were observed for all other explanatory variables on CRP responses. The effect of explanatory variables on HPX responses are detailed in Table 3. We found a significant association between HPX responses and time (0.005 mmol/L H_2O_2; $p = 0.020$). HPX responses were lower compared with measures taken at GD-1 during Case 1 (-0.18 mmol/L H_2O_2; $p = 0.057$), and higher at Control 2 (0.26 mmol/L H_2O_2; $p = 0.055$), albeit of borderline significance (Figure 1B). No significant relationships were observed for all other explanatory variables and HPX.

4. Discussion

The primary aim of this study was to assess the efficacy of an acute protective protocol (curcumin supplementation) on blood biomarkers of inflammation and pro-oxidant status during the in-season competitive phase of the EPL. The principal findings were that curcumin ingestion had no significant effect on CRP, and had borderline significant effects on HPX responses ($p = 0.057$). However, the magnitude of this change (-0.18 mmol/L H_2O_2) does not appear to be physiologically relevant, based on the previously published critical difference value for this assay (Lewis et al., 2016), suggesting that at a group level curcumin ingestion using the dose and protocol prescribed may not be effective for attenuating inflammation and pro-oxidant status within the setting of elite professional soccer. To our knowledge, this is the first study to investigate the efficacy of a nutritional intervention aimed at reducing blood biomarkers of recovery in professional soccer players competing in the EPL.

We report that HPX levels significantly increase within-season in apparently healthy players and that curcumin ingestion at the dose prescribed is not effective for attenuating biomarker responses in elite soccer players. Curcumin has been reported to downregulate the transcriptional activity of nuclear factor-kappa B (NF-kB), a key regulator of the inflammatory response, and upregulate nuclear factor erythroid 2 related factor 2 (Nrf2), the 'master regulator' of antioxidant enzymes (Sahin et al., 2016). Therefore, by simultaneously blocking the proinflammatory response and activating endogenous anti-oxidants, curcumin ingestion may act to control the regulation of inflammation during

Table 1: Summary Statistics for CRP (mg/L), HPX (mmol/L H_2O_2) and THIR (m) by Study Stage and Testing Time.

Stage	**Control 1 (August/September)**		**Case 1 (September/October)**		**Control 2 (November)**		**Case 2 (November/December)**	
	Pre (n = 87)	Post (n = 59)	Pre (n = 55)	Post (n = 41)	Pre (n = 33)	Post (n = 7)	Pre (n = 72)	Post (n = 45)
CRP								
Mean (SD)	1.62 (1.52)	2.15 (1.60)	1.48 (0.92)	1.91 (1.30)	1.49 (0.98)	2.72 (1.40)	1.50 (0.92)	2.21 (1.42)
Median	0.98	1.25	1.04	1.44	1.07	3.10	1.06	1.65
[Min, Max]	[0.76, 8.89]	[0.80, 7.75]	[0.81, 5.21]	[0.77, 7.22]	[0.74, 4.64]	[0.94, 4.10]	[0.79, 4.73]	[0.91, 7.48]
HPX								
Mean (SD)	1.55 (0.31)	1.64 (0.29)	1.75 (0.37)	1.74 (0.38)	1.67 (0.34)	1.95 (0.34)	1.79 (0.46)	1.78 (0.37)
Median	1.54	1.60	1.70	1.70	1.63	1.94	1.71	1.73
[Min, Max]	[1.22, 2.61]	[1.22, 2.46]	[1.22, 2.68]	[1.26, 3.11]	[1.22, 2.68]	[1.50, 2.47]	[1.22, 3.52]	[1.22, 2.46]
THIR								
Mean (SD)	446 (207)	454 (217)	391 (233)	473 (194)	446 (331)	468 (369)	388 (199)	415 (200)
Median	477	450	479	525	473	456	420	409
[Min, Max]	[49.0, 920]	[66.3, 920]	[14.6, 713]	[38.1, 713]	[7.83, 1100]	[7.83, 970]	[10.2, 822]	[17.2, 822]

Note: n**,** number of participants; SD, Standard Deviation; Min, Minimum; Max, Maximum; CRP, C-reactive protein; HPX, hydroperoxides; THIR, total high intensity running

Table 2: The estimated effect of explanatory variables on C-reactive protein (CRP) (mg/L) responses adjusted for the effect of game and subject by fitting linear mixed effects models.

Explanatory Variable	**Estimate**	**Standard Error**	***p***
Pre- (vs Post-) game	-0.860	1.132	0.453
Stage (Case 1)[a]	-0.380	0.564	0.512
Stage (Control 2)[a]	-0.299	0.734	0.691
Stage (Case 2)[a]	-0.671	0.941	0.491
GD +1days[b]	2.021	1.135	0.084
GD +2days[b]	1.147	1.132	0.319
GD +3days[b]	1.229	1.197	0.311
Time (Days)	0.010	0.009	0.311
THIR (m)	0.000	0.000	0.276

Note: [a]in comparison to Control 1; [b]in comparison to Game Day (GD)+4; THIR, Total high intensity running; GD, Game Day

Table 3: The estimated effect of explanatory variables on hydroperoxides (HPX) (mmol/L H_2O_2) responses adjusted for the effect of game and subject by fitting linear mixed effects models.

Explanatory Variable	**Estimate**	**Standard Error**	***p***
Pre- (vs Post-) game	0.095	0.119	0.426
Stage (Case 1)[a]	0.000	0.119	0.999
Stage (Control 2)[a]	-0.277	0.153	0.089
Stage (Case 2)[a]	-0.272	0.196	0.187
Time (Days)	0.005	0.002	**0.020**
THIR (m)	-0.000	0.000	0.613
Post-Test Day[b]	-0.016	0.004	0.721
Post- (vs Pre-): Stage (Case 1)[a]	-0.181	0.095	0.057
Post- (vs Pre-): Stage (Control 2)[a]	0.255	0.132	0.055
Post- (vs Pre-): Stage (Case 2)[a]	-0.077	0.007	0.288

Note: [a]in comparison to Control 1; [b]in comparison to Game Day (GD)+1; THIR**,** Total high intensity running*;* significant effects (p < 0.05) are displayed in bold

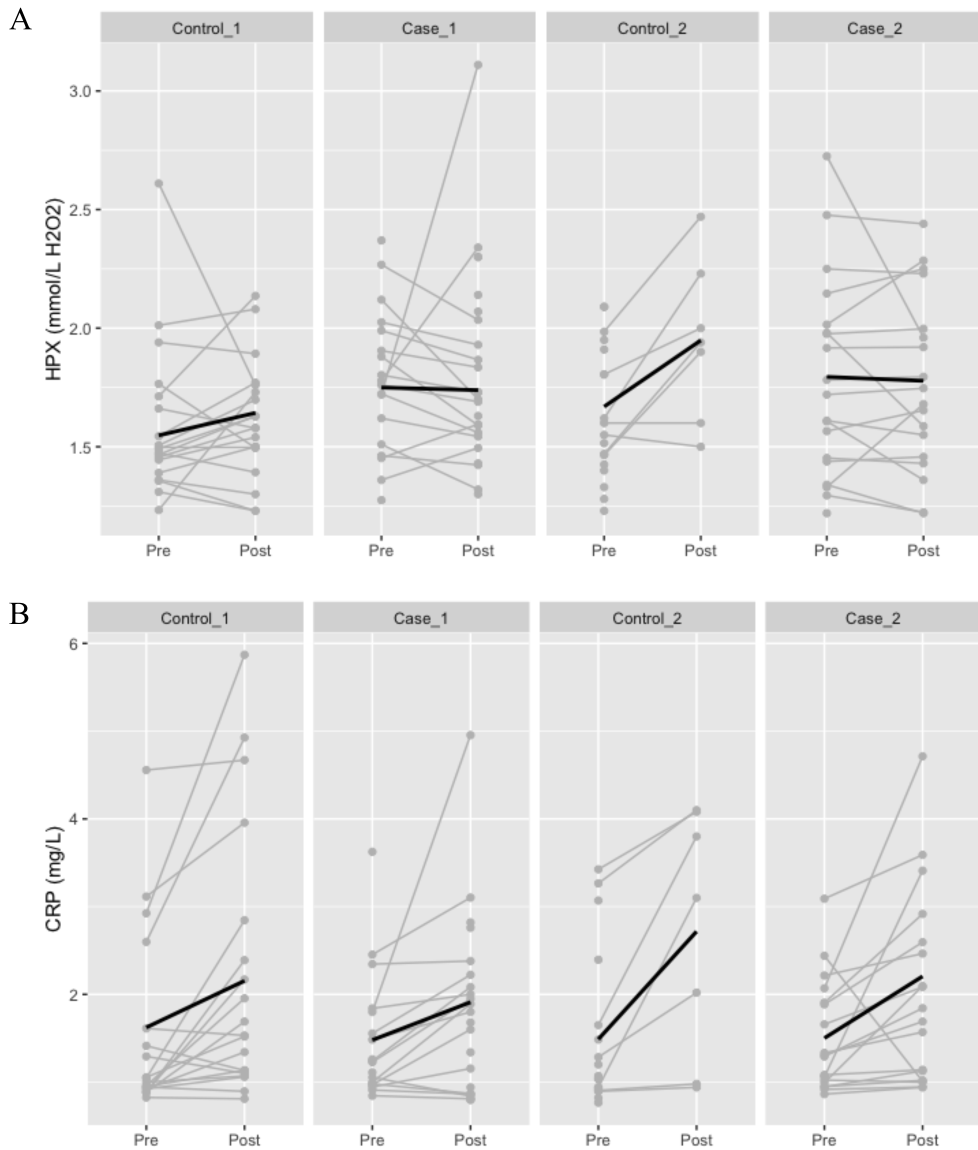

Figure 1: (A) Plots of players average C-Reactive Protein (CRP) (mg/L) trajectory over stage. (B) Plots of players average hydroperoxides (HPX) (mmol/L H_2O_2) trajectory over stage. Black lines represent group mean, grey lines represent player averages. Stages: Control_1 (August/September), Case_1 (September/October), Control_2 (November), Case_2 (November/December).

periods of high demand in the elite soccer player. However, in the current study, we report no significant differences between conditions for mean CRP values (Figure 1A). Indeed, reports are inconsistent with regards to exercise induced inflammation in the literature (Heaton et al., 2017; Suhett et al., 2020). In agreement with our findings, Drobnic et al. (2014) (400 mg daily dose for 48 hours prior to and 24 hours after a downhill running test in moderately active males) and Sciberras et al. (2015) (500 mg daily dose for 72 hours and immediately prior to a 2 hour cycling test in recreationally active males) have shown that whilst post-exercise increases in markers of inflammation have tended to be lower in curcumin treatment groups, significant reductions in inflammation with curcumin supplementation are lacking. In contrast, we observed reductions in mean HPX levels during the Case 1 phase (Figure 1B), albeit of borderline significance, suggesting that curcumin supplementation may attenuate exercise induced oxidative stress, a finding which is corroborated by previous research (Chilelli et al., 2016; Takahashi et al., 2013). However, when we consider the magnitude of this change (Table 3), physiological relevance appears questionable based on the previously published critical difference value for this assay (Lewis et al., 2016). The discrepancy between our findings and previous literature demonstrating statistically significant changes may be due to a combination of factors including the training and dietary status of the population investigated, the biomarker assays measured and timing of the draw, and several limitations associated with the current study.

To the authors knowledge, this is the first study investigating the utility of curcumin supplementation in elite soccer players. Indeed, given the recognised differences in inflammatory responses between athletes and non-athletes (Gokhale et al., 2007; Handzlik et al., 2013), caution is necessary when extrapolating findings from previous research investigating the utility of curcumin in non-athletes to the professional soccer player. Evidence suggests that professional soccer players upregulate anti-oxidant enzymes during a season (Silva et al., 2014), thus potentially protecting well recovered players from excessive oxidative damage during subsequent competitions and training sessions. It is plausible that this upregulation may be sufficient to limit excessive inflammatory mediator production and therefore elite soccer players may have less need to use anti-oxidant supplements than non-athletes, especially when athletes may be consuming high polyphenolic diets. Indeed, focusing on a well-balanced diet including fruits and vegetables to counteract inflammation and oxidative stress may be more appropriate for the elite soccer player than supplementing with individual antioxidants/anti-inflammatory compounds, as there seems to be no evidence at this time to suggest that consumption of fruits and vegetables blunts exercise-induced adaptations (Heaton et al., 2017). Furthermore, human studies have shown that the intake of fruits and vegetables is associated with a decrease in the levels of systemic inflammatory markers, such as Interleukin (IL)-4, IL-6, IL-8, IL-13, Tumor Necrosis Factor-alpha (TNF-α) and CRP (Sureda et al., 2014) and increases in anti-inflammatory cytokines in well trained athletes (McAnulty et al., 2011).

The wide heterogeneity in CRP (Figure 1A) and HPX responses (Figure 1B) may also provide important clues about why the study results are inconsistent. Indeed, studies have shown that the efficacy of antioxidants is affected by inter-individual variability in redox state, which is dependant, among other factors, on the training and nutritional status of the athlete (Kawamura et al., 2018). Recent reports have recognised the importance of identifying and correcting redox deficiencies in athletes which may occur as a result of low fruit and vegetable intake (Pedlar et al., 2019; Plunkett et al., 2010; Watson et al., 2005). Plunkett et al. (2010) observed increased resting and exercise induced inflammation alongside increased RPE in endurance trained males in response to a two week dietary anti-oxidant restriction. Moreover, emerging evidence suggests that antioxidant supplements improve performance and oxidative stress only when administered to deficient individuals (Margaritelis et al., 2020). Therefore, the optimal intervention approach should involve the individualized examination of redox and inflammation status in athletes. This would allow for the identification of responsive phenotypes and the detection of meaningful physiological changes in individual data, by constructing individualized adaptive reference ranges (Roshan et al., 2021), resulting in the administration of the appropriate antioxidant supplementation at the appropriate time. Future studies should look to implement this targeted approach in elite sport.

The lack of significant changes in biomarker responses may also be explained by the assays measured in the current study. Higher concentrations of individual antioxidant enzymes as opposed to total anti-oxidant capacity have been found in rodents following curcumin supplementation (Avci et al., 2012), suggesting that curcumin's anti-inflammatory effects may potentially be tissue and/or enzyme specific (Basham et al., 2020). Furthermore, despite observing no significant reduction in serum levels of IL-6, McFarlin et al. (2016) reported a 25% decrease in circulating levels of the inflammatory cytokines TNF-α and IL-8 following muscle damaging exercise in a group of healthy participants. Thus, the lack of measurements of a wider range of inflammatory biomarkers and anti-oxidant enzymes could potentially be a limiting factor in the current study.

For practical reasons (i.e., financial and time constraints), we did not measure anti-oxidant status, thus, we potentially missed capturing the impact of curcumin on the players' plasma anti-oxidant capacity. Similarly, we did not assess whether curcumin's serum concentration had sufficiently increased after the supplementation regimen so as to produce biological effects (Suhett et al., 2020). Considering the field-based nature of the present study, obvious limitations include the inability to blind the players and staff to the supplementation regimen and control the players' dietary intake. However, the use of control versus intervention groups is generally un-feasible at the elite level as only a single population benefits from the intervention (Bongiovanni et al., 2020; Carling et al., 2018), and restricting an athlete of important dietary nutrients during a competitive season is counter-intuitive in a high performance environment if the goal is to conduct applied research. Indeed, Bongiovanni et al. (2020) suggest that applied research should replicate how athletes actually utilize supplements in a real-world scenario in order to inform practice, and thus, the nature of the study (i.e., highly-trained EPL players in a 'real-world' setting) strengthens the ecological validity and novelty of our data. The use of an interrupted time series design may therefore be considered novel, however, it is also possible that the training status and workload (e.g., THIR) of the athlete during the different stages of the intervention may have influenced the regulation of inflammation to a greater extent than the supplementation regimen.

Athlete belief is another important consideration in the application of an intervention (Halson et al., 2013; Howatson et al., 2016). Failure to capture the athletes perception of the supplementation regimen and whether or not they felt it was effective in reducing the symptoms of muscle damage and inflammation (e.g., muscle soreness) is therefore another limitation in the current study. Additionally, capturing dietary data would have strengthened our analysis and allowed us to highlight individuals with dietary deficiencies. Future studies with larger samples, and multiple curcumin dosages are warranted to investigate if different curcumin regimens can lead to statistically different CRP and HPX levels in the elite soccer player.

5. Conclusion

To our knowledge, this is the first study to investigate the efficacy of a nutritional intervention aimed at reducing biomarkers of inflammation and pro-oxidant status in professional soccer players competing in the EPL. Our data demonstrate that curcumin ingestion at the dose and protocol prescribed is not effective for attenuating biomarker responses in elite soccer players competing in the EPL. Future studies should look to implement a more targeted approach to anti-oxidant supplementation in elite sport, involving the individualized examination of redox and inflammation status in athletes to allow for the identification of responsive phenotypes and the detection of meaningful physiological changes in individual data. This may also help progress away from a 'one-size fits all' approach to the use of anti-oxidant/anti-inflammatory supplementation, which is often adopted in elite sport, by identifying periods where an individual may require (or not require) intervention, resulting in the administration of anti-inflammatory interventions at the appropriate time.

Highlights

- The present investigation questions the efficacy of curcumin ingestion, using the dose and protocol prescribed (total dose of 1000 mg of curcumin, as recommended by the manufacturer, the morning of game day -2 (GD-2), game day -1 (GD-1) and immediately post-game during each supplementation period) for the purpose of reducing inflammation and pro-oxidant status in elite soccer players when following their habitual diets.
- Future studies should look to implement a more targeted approach to anti-oxidant supplementation in elite sport, involving the individualized examination of redox and inflammation status in athletes to allow for the identification of responsive phenotypes and the detection of meaningful physiological changes in individual biomarker data.

Conflict of Interest

The authors declare the following conflicts of interest relevant to the content of this study. Diarmuid Daniels, Nathan A. Lewis, Georgie Bruinvels, Andrew Barr and Charles R. Pedlar are employees or consultants with Orreco Ltd. John Newell is the Principal Investigator of the Orreco Ltd-funded research project in the Insight Centre for Data Analytics, University of Galway. Orreco Ltd provide blood biomarker services to elite athletes.

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References

Avci, G., Kadioglu, H., Sehirli, A. O., Bozkurt, S., Guclu, O., Arslan, E., & Muratli, S. K. (2012). Curcumin protects against ischemia/reperfusion injury in rat skeletal muscle. *Journal of Surgical Research*, *172*(1), e39-e46.

Basham, S. A., Waldman, H. S., Smith, J., Krings, B. M., Lamberth, J., Smith, J. W., & McAllister, M. J. (2019). Effect of curcumin supplementation on exercise-induced oxidative stress, inflammation, muscle damage, and muscle soreness. *Journal of Dietary Supplements*, *17*(4), 401-414.

Becker, M., Sperlich, B., Zinner, C., & Achtzehn, S. (2020). Intra-individual and seasonal variation of selected biomarkers for internal load monitoring in U-19 soccer players. *Frontiers in Physiology*, *11*, 1-13.

Bongiovanni, T., Genovesi, F., Nemmer, M., Carling, C., Alberti, G., & Howatson, G. (2020). Nutritional interventions for reducing the signs and symptoms of exercise-induced muscle damage and accelerate recovery in athletes: Current knowledge, practical application and future perspectives. *European Journal of Applied Physiology*, *120*(9), 1965-1996.

Carling, C., Lacome, M., McCall, A., Dupont, G., Le Gall, F., Simpson, B., & Buchheit, M. (2018). Monitoring of post-match fatigue in professional soccer: Welcome to the real world. *Sports Medicine*, *48*(12), 2695-2702.

Catterson, P., Moore, B., Hodgson, A., Lewis, N., Newell, J., & Charles, P. (2014). A case study of two premiership footballers with sickle cell trait using novel tests of redox homeostasis. *British Journal of Sports Medicine*, *48*(7), 577.

Chilelli, N. C., Ragazzi, E., Valentini, R., Cosma, C., Ferraresso, S., Lapolla, A., & Sartore, G. (2016). Curcumin and boswellia serrata modulate the glyco-oxidative status and lipo-oxidation in master athletes. *Nutrients*, *8*(11), 1-9.

Drobnic, F., Riera, J., Appendino, G., Togni, S., Franceschi, F., Valle, X., Pons, A., & Tur, J. (2014). Reduction of delayed onset muscle soreness by a novel curcumin delivery system (Meriva®): A randomised, placebo-controlled trial. *Journal of the International Society of Sports Nutrition*, *11*(1), 1-10.

Gokhale, R., Chandrashekara, S., & Vasanthakumar, K. C. (2007). Cytokine response to strenuous exercise in athletes and non-athletes – an adaptive response. *Cytokine*, *40*(2), 123-127.

Halson, S. L., & Martin, D. T. (2013). Lying to win – placebos and sport science. *International Journal of Sports Physiology and Performance*, *8*(6), 597-599.

Handzlik, M. K., Shaw, A. J., Dungey, M., Bishop, N. C., & Gleeson, M. (2013). The influence of exercise training status on antigen-stimulated IL-10 production in whole blood culture and numbers of circulating regulatory T cells. *European Journal of Applied Physiology*, *113*, 1839-1848.

Heaton, L. E., Davis, J. K., Rawson, E. S., Nuccio, R. P., Witard, O. C., Stein, K. W., Baar, K., Carter, J. M., & Baker, L. B. (2017). Selected in-season nutritional strategies to enhance recovery for team sport athletes: A practical overview. *Sports Medicine*, *47*, 2201-2218.

Howatson, G., Leeder, K., & Van Someren, K. (2016). The BASES expert statement on athletic recovery strategies. *The Sport and Exercise Scientist*, Issue 48, 6-7.

Ispirlidis, I., Fatouros, I. G., Jamurtas, A. Z., Nikolaidis, M. G., Michailidis, I., Douroudos, I., Margonis, K., Chatzinikolau, A., Kalistratos, E., Katrabasas, I., Alexious, V., & Taxildaris, K. (2008). Time-course of changes in inflammatory and performance responses following a soccer game. *Clinical Journal of Sport Medicine*, *18*(5), 423-431.

Kawamura, T., & Muraoka, I. (2018). Exercise-induced oxidative stress and the effects of antioxidant intake from a physiological viewpoint. *Antioxidants*, *7*(9), 1-19.

Lewis, N. A., Newell, J., Burden, R., Howatson, G., & Pedlar, C. R. (2016). Critical difference and biological variation in biomarkers of oxidative stress and nutritional status in athletes. *PLoS One*, *11*(3), 1-12.

Lewis, N. A., Simpkin, A. J., Moseley, S., Turner, G., Homer, M., Redgrave, A., Pedlar, C. R., & Burden, R. (2020). Increased oxidative stress in injured and ill elite international Olympic rowers. *International Journal of Sports Physiology and Performance*, *15*(5), 625-631.

Margaritelis, N. V., Paschalis, V., Theodorou, A. A., Kyparos, A., & Nikolaidis, M. G. (2020). Antioxidant supplementation, redox deficiencies and exercise performance: A falsification design. *Free Radical Biology and Medicine*, *158*, 44-52.

Markworth, J. F., Maddipati, K. R., & Cameron-Smith, D. (2016). Emerging roles of pro-resolving lipid mediators in immunological and adaptive responses to exercise-induced muscle injury. *Exercise Immunology Review*, *22*, 110-134.

McFarlin, B. K., Venable, A. S., Henning, A. L., Sampson, J. N. B., Pennel, K., Vingren, J. L., & Hill, D. W. (2016). Reduced inflammatory and muscle damage biomarkers following oral supplementation with bioavailable curcumin. *BBA Clinical*, *5*, 72-78.

Nicol, L. M., Rowlands, D. S., Fazakerly, R., & Kellett, J. (2015). Curcumin supplementation likely attenuates delayed onset muscle soreness (DOMS). *European Journal of Applied Physiology*, *115*, 1769-1777.

Owens, D. J., Twist, C., Cobley, J. N., Howatson, G., & Close, G. L. (2019). Exercise-induced muscle damage: What is it, what causes it and what are the nutritional solutions? *European Journal of Sport Science*, *19*(1), 71-85.

Plunkett, B. A., Callister, R., Watson, T. A., & Garg, M. L. (2010). Dietary antioxidant restriction affects the inflammatory response in athletes. *British Journal of Nutrition*, *103*(8), 1179-1184.

Roshan, D., Ferguson, J., Pedlar, C. R., Simpkin, A., Wyns, W., Sullivan, F., & Newell, J. (2021). A comparison of methods to generate adaptive reference ranges in longitudinal monitoring. *PLoS One*, *16*(2), 1-19.

Sahin, K., Pala, R., Tuzcu, M., Ozdemir, O., Orhan, C., Sahin, N., & Juturu, V. (2016). Curcumin prevents muscle damage by regulating NF-κB and Nrf2 pathways and improves performance: An in vivo model. *Journal of Inflammation Research*, *29*(9), 147-154.

Sciberras, J. N., Galloway, S. D. R., Fenech, A., Grech, G., Farrugia, C., Duca, D., & Mifsud, J. (2015). The effect of turmeric (Curcumin) supplementation on cytokine and inflammatory marker responses following 2 hours of endurance cycling. *Journal of the International Society of Sports Nutrition*, *12*(1), 1-10.

Silva, J. R., Rebelo, A., Marques, F., Pereira, L., Seabra, A., Ascensão, A., & Magalhães, J. (2014). Biochemical impact of soccer: An analysis of hormonal, muscle damage, and redox markers during the season. *Applied Physiology, Nutrition, and Metabolism*, *39*(4), 432-438.

Suhett, L. G., de Miranda Monteiro Santos, R., Silveira, B. K. S., Leal, A. C. G., de Brito, A. D. M., de Novaes, J. F., & Lucia, C. M. D. (2021). Effects of curcumin supplementation on sport and physical exercise: A systematic review. *Critical Reviews in Food Science and Nutrition*, *61*(6), 946-958.

Sureda, A., Tejada, S., del Mar Bibiloni, M., Tur, J. A., & Pons, A. (2014). Polyphenols: Well beyond the antioxidant capacity: Polyphenol supplementation and exercise-induced oxidative stress and inflammation. *Current Pharmaceutical Biotechnology*, *15*(4), 373-379.

Szymanski, M. C., Gillum, T. L., Gould, L. M., Morin, D. S., & Kuennen, M. R. (2018). Short-term dietary curcumin supplementation reduces gastrointestinal barrier damage and physiological strain responses during exertional heat stress. *Journal of Applied Physiology*, *124*(2), 330-340.

Takahashi, M., Suzuki, K., Kim, H. K., Otsuka, Y., Imaizumi, A., Miyashita, M., & Sakamoto, S. (2014). Effects of curcumin supplementation on exercise-induced oxidative stress in humans. *International Journal of Sports Medicine*, *35*(06), 469-475.

Tanabe, Y., Chino, K., Ohnishi, T., Ozawa, H., Sagayama, H., Maeda, S., & Takahashi, H. (2019). Effects of oral curcumin ingested before or after eccentric exercise on markers of muscle damage and inflammation. *Scandinavian Journal of Medicine & Science in Sports*, *29*(4), 524-534.

Watson, T. A., Callister, R., Taylor, R. D., Sibbritt, D. W., MacDonald-Wicks, L. K., & Garg, M. L. (2005). Antioxidant restriction and oxidative stress in short-duration exhaustive exercise. *Medicine and Science in Sports and Exercise*, *37*(1), 63-71.