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Physiological outcomes of physical activity interventions in persistent postconcussive symptoms: a scoping review protocol

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ABSTRACT

There are limited therapeutic options for patients with persistent postconcussive symptoms (PPCSs). Most PPCS assessments focus on subjective measures of progression and symptom monitoring. While early exercise interventions for rehabilitation are now considered best practice for acute concussion, no comprehensive review exists on how physical activity objectively and physiologically affects outcomes in PPCS. This scoping review protocol outlines the methods to identify the efficacy of therapeutic exercise interventions for PPCS, emphasising their impact on physiological parameters, including cardiovascular autonomic responses and cerebral autoregulation. Using the Patient, Intervention, Comparison and Outcome (PICO) framework, we will include all studies presenting original data. Narrative summaries will provide clinicians. An initial search in Medline/EMBASE/PubMed, Cochrane Library, PsycINFO, Web of Science and Scopus will be completed. Key parameters from each study will be extracted, tabulated and discussed in a narrative inquiry. The study references will be reviewed for additional studies meeting the inclusion criteria. Future research applications from the findings will be emphasised. After completion of the review, the results will be stratified by type of physical activity as the intervention, emphasising the physiological outcomes. Mapping these findings will allow us to identify the key research priorities for future studies. Findings will be shared with PPCS practitioners and local/national committees and submitted for conferences and publications.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Physical activity interventions are known to have therapeutic effects for patients with acute concussion or persistent post-concussive symptoms (PPCSs).

WHAT THIS STUDY ADDS

⇒ This scoping review protocol will identify changes in objective, physiological markers following exercise interventions in patients with persistent post-concussive symptomsPPCS, thus developing the framework to guide clinical practice and inform standardised rehabilitation protocols.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study will inform clinical rehabilitation by identifying key physiological markers affected by exercise in persistent post-concussive symptoms (PPCS), guiding future treatment and research.

INTRODUCTION

Persistent postconcussive symptoms (PPCSs) occur in individuals who do not recover within the typical 2–4 weeks period following a mild traumatic brain injury (mTBI) or concussion.[1] A concussion is a brain injury resulting from an external mechanical force that disrupts brain function. This is often caused by a direct blow to the head or a force transmitted to the head from another body part. The Glasgow Coma Scale (GCS), commonly used to assess the severity of brain injuries, defines mTBI as an injury with an initial GCS score of 13–15 within 30 min of the injury, indicating a mild level of impairment. The prevalence of PPCS varies, with estimates suggesting that 8%–53% of individuals experience at least one persistent symptom for up to a year following a concussion, highlighting the potential for long-term impacts on recovery and prognosis.[2 3] Symptoms for PPCS include somatic, cognitive and emotional domains[1] and often include headache disorder, anxiety and depression.[4]

Despite growing recognition of PPCS, a thorough understanding of the physiological complications of this condition remains limited. Acute concussion disrupts cellular homoeostasis and triggers metabolic and neurometabolic changes, increasing blood–brain barrier (BBB) permeability,[5–8] often leading to autonomic dysfunction and a heightened risk for sustained autonomic stress.[9] Physiologically, concussion can result in a widespread array of disruptions to normal autonomic physiological function, often leading to altered cerebral autoregulation,

neurovascular coupling (NVC)[10] and cerebrovascular reactivity (CVR).[11] Although the physiological disruptions in acute concussion have been extensively studied, there is a lack of research summarising the specific pathophysiological implications of PPCS.

Measures of autonomic stress often include cardiovascular, neurophysiological and blood biomarkers. Evidence shows that following acute concussion, there is usually reduced heart rate variability (HRV)[12] and blood pressure variability (BPV),[13] as well as altered baroreflex sensitivity (BRS).[13 14] HRV is reflected through changes in heart rate as a response to the autonomic nervous system's adaptability to various stressors. During concussion, depressed HRV may suggest heightened stress or diminished recovery capacity.[14] Complimentary to HRV, BPV represents the fluctuations in blood pressure over time, and BRS is the ability to stabilise blood pressure by adjusting heart rate and vascular resistance in response to changes in blood pressure.[14] Alterations in HRV, BPV and BRS are noted in acute sport-related concussion.[13] For patients with PPCS, similar alterations in BPV have been noted,[15] though large cohort research is limited.

Additionally, elevations in inflammatory markers, such as IL-8, PDGF and TNF, are associated with increased PPCS risk, and protective markers, such as IL-9 and MCP-1, have been more extensively characterised in PPCS.[16] In a series of studies, including those with a history of concussion and persistent symptoms for over a decade following the last injury, cerebral oxygenation is altered during activation of physiological processes, including autoregulation, NVC and CVR.[10 17 18] However, data on neurophysiological markers of cerebral blood flow[19 20] remain limited. As such, it is hypothesised that patients with PPCS will show altered neurophysiological and cardiovascular autonomic nervous system function.

Treatment and rehabilitation options for patients with PPCS have not been well studied. Exercise as an intervention has been identified recently as a primary treatment modality for acute concussion[21] and has been suggested to improve symptoms in PPCS, though this research is limited.[22] Nutritional interventions also show promise to improve symptoms and blood pressure dynamics in PPCS.[23] Notably, no summary is available to identify physiological changes in PPCS following a physical activity intervention. This review aims to fill that gap by summarising existing research on the physiological impact of exercise-based interventions, focusing on changes in markers of autonomic stress, cardiovascular health and neurophysiological outcomes.

METHODS

This review summarises the physiological outcomes of exercise interventions for PPCS across all ages. This includes cases arising not only from sports-related incidents but also from other sources, such as recreational activities, motor vehicle accidents and occupational injuries, which resulted in an eventual PPCS diagnosis.

PATIENT AND PUBLIC INVOLVEMENT

Patients and the public were not involved in this study's design, conduct, recruitment or dissemination.

RESEARCH QUESTION

1. What is the current evidence for exercise-based interventions in managing patients with PPCS?
2. What are the physiological mechanisms that drive their effectiveness?
3. How consistent are the outcomes of these interventions across varied patient demographics, including age, sex, symptoms and comorbidities (eg, anxiety, depression, cardiovascular conditions or prior concussions)

PROTOCOL DESIGN

The Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping reviews was used in drafting this scoping review protocol. This protocol is not registered with PROSPERO as they do not accept scoping review protocols. The 'PICO' approach was applied to identify the specific review parameters. Specifically, p=Patients with PPCS, I=Physical activity, C=None and O=Physiological changes.

Patients

No limitation will be applied regarding age or sex for participants in the included studies, allowing the review to capture a comprehensive group of patients with PPCS across diverse demographics. This acknowledges that PPCS may affect individuals differently based on developmental, physiological and hormonal factors and aims to include a broad range of patient experiences.

All participants must have (1) a diagnosis of PPCS or (2) present with unresolved symptoms of mTBI, as determined by a clinician.

PPCS will have a minimum cut-off period of 10 days postinitial injury for adults, while for children, this period will be extended to at least 4 weeks. This approach will allow consideration of the slower symptom resolution in children due to ongoing brain development and differences in neurophysiological responses, necessitating a longer time frame to accurately identify persistent symptoms. In comparison, adults typically recover 80%–90% of their concussion symptoms within 10–14 days.[24 25]

Intervention

The intervention criterion will include any variety or type of physical activity, encompassing both acute exercise sessions and chronic exercise programs, to capture the different approaches used in managing PPCS.

Comparison

Studies will be included in the review regardless of whether they feature a comparison group, allowing for examining interventions with or without alternative treatments. No meta-analysis will be completed as part of this review.

Outcome

The included studies will require an outcome measure of physiological function. These physiological markers will help us assess autonomic function, or how well the nervous system controls automatic functions like heart rate and blood pressure. Alterations in these markers may explain the prolonged symptoms experienced by individuals with PPCS. There will be no limitation to when the assessment or data collection occurred postdiagnosis. Given that no universally accepted modalities of physical activity are available for recovery from PPCS, all physical activity interventions will be included. A pragmatic approach is required for this review, given the limited number of articles available about this area.

Measures to be extracted include but are not limited to neurophysiological and cardiovascular autonomic assessments. Specifically, examples of such measures include (1) cerebral blood flow measures via transcranial Doppler (such as vessel reactivity, blood flow velocity and pulsatility), (2) cerebral oxygenation (via the use of near-infrared spectroscopy or magnetic resonance imaging) and (3) cardiovascular autonomic function (such as HRV, BPV and BRS).

Finally, we will also study the mechanisms by which physical activity interventions may alter the course of PPCS. Specifically, we will assess key areas that are considered altered in PPCS. These will include dynamic and static cerebral autoregulation (sCA and dCA, respectively), NVC, CVR, and integrity of the BBB. NVC is the brain adjusting blood flow based on neural activity. Similarly, CVR is the capacity of blood vessels in the brain to respond to changes in CO2 levels. dCA and sCA are mechanisms the brain employs to maintain consistent blood flow under varying conditions, safeguarding it from fluctuations in blood pressure. Alterations in these processes, if present, will direct future research. Symptoms will be collected as a secondary outcome; however, their implications will be associated with changes in physiological function. In turn, we can understand if symptom 5 resolution correlates with physiological function, indicating a potential association between relief of autonomic dysfunction and clinical symptoms.

Study design

We will include all prospective and retrospective study designs presenting original data. However, given the novelty of this research, we will not include other reviews or meta-analyses except to review their reference list for additional studies to include. Study abstracts without full text will be included if they present original data. Any available 'grey literature' studies and those published in non-peer-reviewed journals (such as poster abstracts webpages) will also be included, provided they follow the inclusion/exclusion criteria. Studies will be included from database inception to December 2024, using searches in Medline/EMBASE/PubMed, Cochrane Library, PsycINFO, Web of Science and Scopus.

Exclusion criteria

Our criteria will be limited to the following: (1) Only 'mTBI' will be included as our initial diagnosis leading to PPCS. This must be explicitly defined and can include the modalities of mTBI, such as a previous sport-related concussion, non-sport-related concussion, whiplash and other terms about mTBI; (2) There must be a medical diagnosis of PPCS or a statement on how long symptoms have been persistent following the initial mTBI; (3) There must be physiological markers of autonomic nervous system function; (4) All non-human studies will be excluded; (5) All studies with self-diagnosed concussion will be excluded; (6) All review studies will be excluded and (7) All non-English studies will be excluded.

The operational definitions to limit subjectivity and support the categorisation of the variables of interest will be as follows:

Persistent postconcussion symptoms

PPCSs, formerly known as postconcussion syndrome, occur when the symptoms of a concussion last longer than expected (meaning failure of normal clinical recovery within the expected timeline). Therefore, adults with symptoms present for more than 10–14 days and children with symptoms present for more than 4 weeks are defined as having PPCS.[26] While older studies may have used different language to describe PPCS, we will include studies that describe the index insult as an mTBI and modify the terminology to PPCS.[26]

Diverse patient populations

In this scoping review protocol, the range of demographics and medical histories considered are age, gender, severity of the concussion and pre-existing conditions. The review will cover patients across all age groups, including children, adolescents, adults and older adults, as recovery from PPCS may differ with age due to developmental and physiological factors. Sex will be considered to assess differences in PPCS symptoms and to understand if males and females experience any differences in the mTBI sequelae. Lastly, medical histories such as prior concussions, neurological conditions, mental health disorders (eg, depression, anxiety) and other comorbidities will be considered, as they may affect the recovery process of exercise-based interventions.

Exercise-based intervention

As research into PPCS advances, rehabilitative exercises have been recognised as integral for recovery. Although no standardised, universally accepted exercise protocols for rehabilitating PPCS, Haider *et al* have proposed individualised exercise training programs based on their response to the buffalo treadmill and cycle ergometer exercise testing protocol.[27 28] Thus, we will include all exercise-based interventions.

Outcomes of these treatments

Our primary outcomes will be physiological measurements. Specifically, we will include studies that monitor

changes in cerebral haemodynamics (blood flow and oxygenation) and cardiovascular autonomic function (such as HRV, BPV and BRS). Additionally, the outcomes of exercise-based interventions on individuals with PPCS are evaluated by tracking improvements in both physical and concussion symptoms. For example, subsymptom threshold aerobic exercise can also improve symptom burden and quality of life in adults with PPCS.[29] Other outcomes include patients' return to normal daily activities and enhanced quality of life. The effectiveness of treatments will be measured using standardised assessment tools and patient self-reports.

DATA MANAGEMENT

The first author (BD) will conduct the electronic search. All references will be exported to EndNote V.20.

Selection of sources of evidence

Keywords related to PPCS (ie, postconcussive syndrome, long-term concussion symptoms and persistent symptoms of mTBI) and exercise-based rehabilitation (ie, aerobic exercise, cognitive rehabilitation and physiological rehabilitation) will be used. We will also use targeted searches for grey literature (difficult-to-locate or unpublished material) by searching Google or visiting agencies' websites that conduct knowledge synthesis. All study designs will be considered, including qualitative and quantitative methods. However, a physiological outcome measurement must be included per operational definitions.

DATA ITEMS

The lead author will extract and tabulate the following parameters: (1) the country where the study was conducted; (2) the objective/aim of the study (primary and secondary outcomes); (3) the sample size and characteristics of the study population; (4) the study design and methodology; (5) the content of the intervention (description of physical activity); (6) the duration and professions delivering the intervention modalities (optional) and (7) the key physiological findings (describe changes based on primary and secondary outcomes).

DATA CHARTING PROCESS

The scoping review aims to provide an overview or map of the evidence. Due to this, an assessment of the risk of bias of the included evidence is not required.

Expected outcome and impacts

At the current stage, the scoping review will aggregate and synthesise a summary of the evidence, with stratification by type of physiological measurement as the primary outcome. Treatment of PPCS has yet to be standardised, with the varied spectrum of symptoms and physiological dysfunction often requiring personalised treatment approaches. Monitoring progression in patients with PPCS remains a unique challenge. This review examines physical activity's role in PPCS treatment and its effect on autonomic function. The study's findings will have a twofold impact: first, to inform clinical guidelines for PPCS rehabilitation by highlighting the most promising exercise-based treatments and to guide future research that aims to improve patient outcomes and quality of life for those suffering from PPCS.

Contributors BD and JS conceptualised and proposed the review. BD drafted the initial manuscript. All authors contributed to the development of the research questions, study design and methodological framework. CJE and JPN provided critical revisions to the methods and framework. All authors contributed to subsequent revisions and approved the final manuscript. BD and JS are the guarantors of the work, accepting full responsibility for its content, data integrity and decision to publish.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The proposed scoping review collects no primary data; therefore, formal ethics approval is not required. It is assumed that the included studies have gained ethics approval from the appropriate ethics approval boards.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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