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Acute effects of exercise with blood flow restriction on endothelial function in healthy young and older populations: a systematic review

Efeitos agudos do exercício com restrição do fluxo sanguíneo na função endotelial de jovens e idosos saudáveis: uma revisão sistemática

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ABSTRACT

The objective of this review is to identify the acute effects of blood flow restriction (BFR) with vs without exercise on endothelial function in healthy individuals and the changes in endothelial function in young and older adults following different levels of exclusive BFR vs free flow. Systematic searches were performed in the following databases: PubMed, Web of Science, Scopus, and Cochrane Library, from inception to July 17, 2021. The studies included healthy individuals who underwent assessments of endothelial function before and after experimental protocols through endothelium-dependent flow-mediated dilatation. In total, 4890 studies were screened, and 6 studies of moderate-to-high methodological quality (Physiotherapy Evidence Database scores 6 – 10) including 82 subjects (aged 24 – 68 years) were eligible. Overall, flow-mediated dilatation increased in the non-cuffed arm immediately and 15 minutes after exercise, with no change in the cuffed arm (BFR of 60 – 80 mmHg). In protocols without exercise, cuff pressures of 25 – 30 mmHg applied for 30 minutes did not promote changes in the endothelial function, while those > 50 mmHg induced a dose-dependent attenuation of flow-mediated dilatation only in young individuals. A moderate level of BFR appears to have no effect on endothelial function after acute exercise. In non-exercise conditions, reductions in flow-mediated dilatation seem to result from increased retrograde shear provoked by cuff pressures ≥ 50 mmHg in young but not in older adults. An exercise-related increase in antegrade shear rate leads to a greater nitric oxide-mediated vasodilator response. However, BFR appears to attenuate this effect in young but not in older individuals.
Keywords: vasodilation; microvascular blood flow; exercise; health.
PROSPERO: CRD42020219686.

RESUMO

O objetivo desta revisão foi identificar os efeitos agudos da restrição do fluxo sanguíneo (RFS) com vs. sem exercício na função endotelial de indivíduos saudáveis, bem como as alterações na função endotelial em jovens e idosos após diferentes níveis de RFS vs. fluxo livre. Pesquisas sistemáticas foram realizadas nas bases United States National Library of Medicine (PubMed), Web of Science, Scopus e Cochrane Library até 17 de julho de 2021. Os estudos incluíram indivíduos saudáveis que avaliaram a função endotelial antes e após protocolos experimentais, por meio da dilatação mediada por fluxo. Foi selecionado o total de 4.890 estudos, e foram elegíveis seis de moderada a alta qualidade metodológica (Physioterapy Evidence Database 6 – 10 pontos), incluindo 82 indivíduos (24 – 68 anos). No geral, a dilatação mediada por fluxo aumentou no braço sem manguito, imediatamente e 15 minutos após o exercício, sem alteração no braço com manguito (RFS de 60 – 80 mmHg). Em protocolos sem exercício, pressões do manguito de 25 – 30 mmHg aplicadas por 30 minutos não promoveram alterações na função endotelial, enquanto aquelas > 50 mmHg induziram uma atenuação dose-dependente da dilatação mediada por fluxo em indivíduos jovens. Um nível moderado de RFS parece não ter efeito na função endotelial após

uma sessão de exercício. Em condições sem exercício, as reduções na dilatação mediada por fluxo parecem resultar do aumento do cisalhamento retrógrado provocado por pressões do manguito ≥ 50 mmHg em jovens, mas não em idosos. O aumento da taxa de cisalhamento anterógrado relacionada ao exercício leva a maior resposta vasodilatadora mediada pelo óxido nítrico. No entanto, a RFS parece atenuar esse efeito em jovens, mas não em idosos.
Palavras-chave: vasodilatação; microcirculação; exercício; saúde.
PROSPERO: CRD42020219686.

INTRODUCTION

The endothelium plays an important role in the maintenance of vascular homeostasis and regulates cellular adhesion, smooth muscle cell proliferation, fibrinolysis, and inflammation.[1] Endothelial function is influenced by several hemodynamic factors, including the direction and magnitude of shear stress, and exercise has been seen as an important stimulus that alters shear stress patterns and, consequently, endothelial function, thus reducing cardiovascular risk.[2,3]

Acute exposure to oscillatory shear stress, characterized by a large retrograde component, was associated with increased levels of markers of endothelial cell apoptosis, eliciting a pro-inflammatory and pro-atherogenic endothelial phenotype.[4] This phenomenon has been studied in the past few years by means of models that apply inflated tourniquet pressure around the limbs.[4-9] Flow-mediated dilatation (FMD) is a commonly used method to identify endothelial dysfunction, which is considered the earliest stage of atherogenesis.[9] FMD assesses arterial diameter in response to 5-min ischemia, the so-called reactive hyperemia (ie, increases in blood flow associated with shear stress),[10-12] which reflects endothelial-derived nitric oxide (NO) bioavailability. The dose-response relationship between magnitude of blood flow restriction (BFR), either associated with exercise or not, and FMD reduction still needs to be better understood, especially in different age groups.[6,7] Establishing this relationship is important because of the strong association between aging and endothelial dysfunction.[13]

Although shear stress has been recognized as an important factor responsible for exercise-induced vascular adaptations,[14-16] BFR can disturb blood flow and alter shear stress patterns,[4-9] thus mitigating the beneficial effects of physical exercise on vascular function.[17] This is particularly relevant considering the increased interest in a novel modality of physical training that combines exercise and BFR. The BFR training has been acknowledged as an intervention capable of enhancing the metabolic signaling pathways associated with hypertrophy and strength gain in groups with poor tolerance to exercise with higher loads, such as older adults,[18] patients with orthopedic diseases,[19] and other frail populations.[20,21]

Previous trials comparing the effects of different levels and periods of BFR in the presence or absence of exercise on endothelial function produced divergent results.[22] Some trials have demonstrated that BFR exercise may lead to enhanced vascular reactivity such as FMD responses,[15] while others failed to demonstrate benefits to endothelial function.[17,23,24] Several factors may help explain those mixed findings, such as age, sex, exercise modality, BFR protocols, and methods to assess vascular function.[7,15,23]

Investigating the acute responses of BFR on the endothelium can provide insight into the causes of longer-term adaptation, which will expand the knowledge of this type of intervention and its clinical applications, especially in populations with limitations to higher loads. Thus, the objective of this systematic review is to identify the acute effects of BFR with vs without exercise on endothelial function in healthy individuals. In addition, we examine the changes in endothelial function in young and older adults following different levels of BFR (without exercise) vs free flow. For this purpose, the magnitude of endothelium-dependent FMD was adopted as the main indicator of endothelial health. Our hypothesis is that BFR acutely promotes negative effects on endothelial function only in young subjects. Furthermore, when compared to BFR alone, BFR associated with exercise is believed to lead to less deleterious effects on the vessel.

METHODS

This systematic review is consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[25] and was registered on the International Prospective Registry of Systematic Reviews (PROSPERO) database under number CRD42020219686. Because it is a systematic review, this study did not involve human subjects and did not require ethical committee approval.

Search strategy and data sources

For the identification of relevant studies, multiple electronic databases (PubMed, Web of Science, Scopus, and Cochrane Library) were searched from inception until July 17, 2021.

A search strategy using the terms "blood flow restriction" OR "vascular occlusion" OR "kaatsu" OR "blood occlusion" OR "blood flow occlusion" OR "venous restriction" OR "restricted blood flow" OR "restricted venous blood flow" AND "vascular" OR "endothelial" OR "retrograde" AND "exercise" identified potentially relevant reports written in English.

Selection criteria

Qualifying trials complied with the PICOS (acronym for patient, intervention, comparison, outcome, and study design) strategy and included the following: adult populations (> 18 years); at least one group performing an acute dynamic handgrip exercise with BFR (until 60 min after cessation of the exercise) and a non-exercise control or comparison group; and endothelial function assessed by FMD before and after intervention for the BFR and control groups. We excluded animal, epidemiological, pharmacological, and review studies; trials including samples under medication influencing vascular function or blood flow; trials involving smokers, alcoholics, or drug addicts; and trials involving diet, drug, environmental, or supplemental interventions in addition to BFR and/or exercise. Since endothelial dysfunction rarely occurs alone (ie, clusters of metabolic or cardiovascular risk factors), studies that included populations exhibiting clinical conditions related to cardiovascular risk (eg, cancer, HIV/AIDS) were excluded. We adopted the same exclusion criteria for studies including samples of young and older individuals.

Data extraction and study outcomes

Potentially relevant reports were screened in duplicate (by KGL and GGC) first by title, then by title and abstract, and lastly by full-text review. Reference lists of included studies, recent reviews, and meta-analyses were searched for additional qualifying reports. A third investigator (RBO) arbitrated any disagreements in coding. To assess the reliability of study inclusion, double coding for 20 randomly selected abstracts was assessed by Cohen's kappa ($\kappa = 1.0$; $p < 0.05$). Excluded studies were re-screened as a quality control measure.

Extracted data included (but were not restricted to) variables of age, sex/gender, clinical status, exercise characteristics (intensity, duration, and mode), BFR characteristics (magnitude of cuff pressure, duration, and cuff placement), FMD outcomes, and study quality. Study quality was assessed by the Physiotherapy Evidence Database (PEDro) scale, a 10-point checklist with higher scores indicating better study quality.[26] Two coders independently performed data extraction and exhibited high inter-rater reliability (mean Cohen's $\kappa = 1.0$).

RESULTS

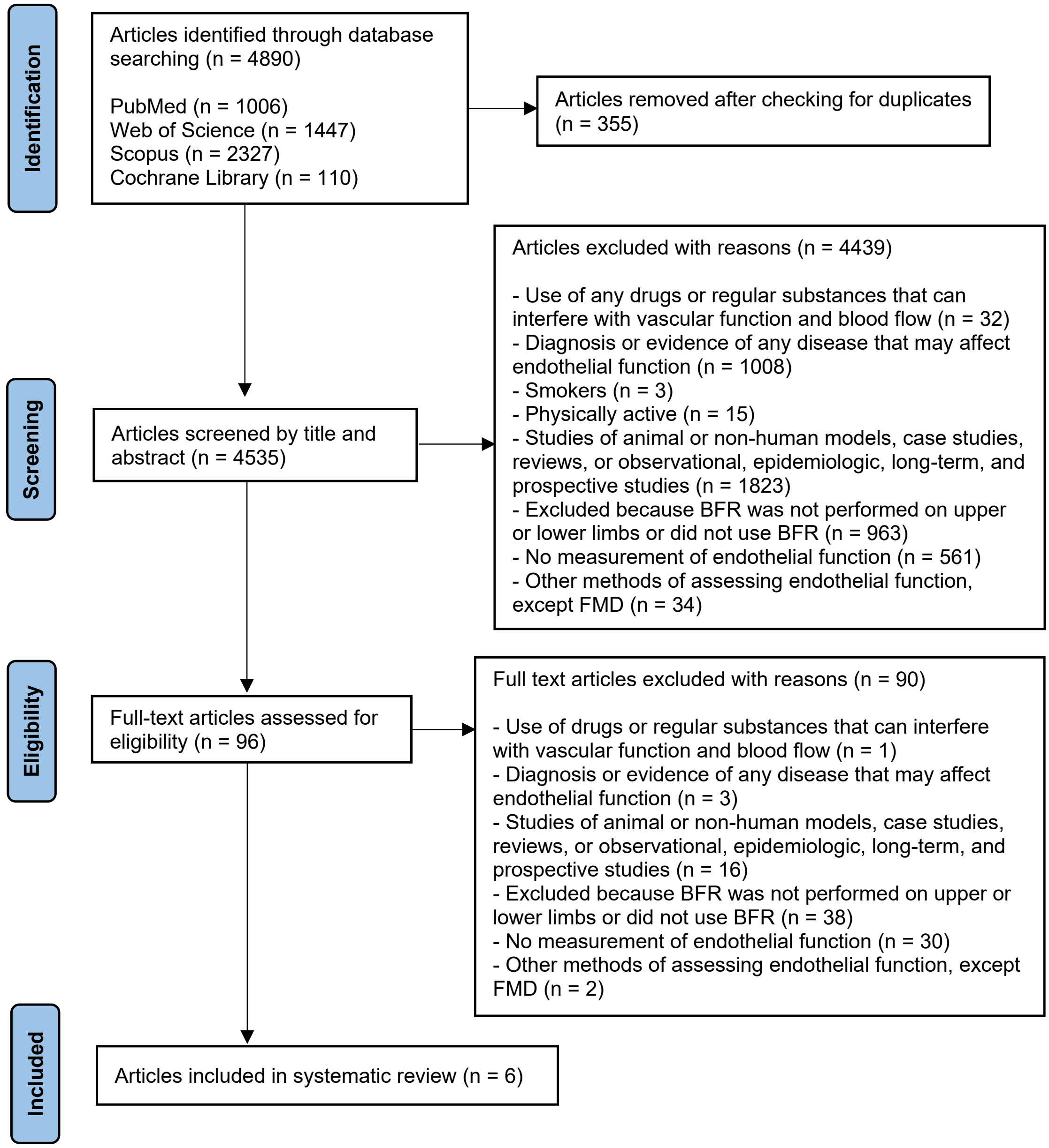
Study selection and quality

Figure 1 shows how reports were selected for the systematic review. Of the initially identified 4890 studies, only 6 trials reporting BFR and FMD at pre- and post-intervention conditions satisfied the eligibility criteria. Of those, one was conducted in Brazil, two in the Netherlands, and three in the United Kingdom.[6,7,9,17,27,28] The trials were of moderate methodological study quality (all studies scored 6 points on PEDro scale), mostly because of the nature of BFR intervention – in general, groups were not randomized, and participants or researchers were not blinded to the BFR or exercise interventions.

Study characteristics and major outcomes

Table 1[6,7,9,17,27,28] depicts the characteristics and outcomes of the studies included in the systematic review. Two studies compared changes in endothelial function following exercise with vs without BFR and included, in total, 19 young men (aged 28 ± 7 years) who were healthy (no cardiovascular or metabolic disease and/or no use of any medication that could influence the cardiovascular system) and recreationally active (< 150 min/week of moderate-intensity physical activity or 75 min/week of high-intensity physical activity).[17,27] Both trials applied low-intensity dynamic handgrip exercise (1 to 2 kg or 60% of maximum voluntary contraction), used moderate levels of BFR (60 or 80 mmHg) through cuffs placed on the forearms, and assessed the brachial artery vasodilation response. Cuff pressure duration ranged from 20 to 30 min, and the non-cuffed arm served as a control limb. FMD in the non-cuffed arm increased immediately[27] and 15 min after exercise,[17] while no significant change occurred in the cuffed arm.[17,27] After 60 min, FMD returned to baseline values with no difference between limbs.[17] No adverse effects were reported during exercise sessions.[17,27]

Four studies evaluated changes in endothelial function at different levels of BFR without exercise, including, in total, 48 young subjects (aged 24 to 27 years)[6,9,28] and 15 older subjects (aged 68 ± 9 years)[7] who were healthy and recreationally active. The older adults had a body mass index of 26.2 ± 3.4 kg/m^2 and no diagnosis of cardiovascular disease or severe hypertension. The studies applied low-to-moderate levels of BFR (25–75 mmHg) on the forearms, upper arm, or thigh.[6,7,9,28] Cuff pressure lasted 30 min, and the non-cuffed arm was used as a control limb.[6,7,9,28] All trials assessed FMD in the brachial artery, and two studies performed additional assessments on the femoral artery.[6,7] Overall, cuff pressures below 30 mmHg did not alter FMD, while pressures greater



BFR: blood flow restriction; FMD: flow-mediated dilatation.

FIGURE 1. Flow diagram for the inclusion of trials in the review.

than 50 mmHg induced a dose-dependent reduction in endothelial function in young[6,9,28] but not in older individuals.[7]

DISCUSSION

This systematic review summarizes the results of trials investigating the acute effects of BFR applied at different magnitudes with and without exercise on endothelial function in young and older individuals. Although limited in number, the studies accumulated evidence indicating that an acute increase in anterograde shear rate promoted by exercise leads to improvements in FMD in healthy young individuals. Conversely, exercise performed with BFR seems to attenuate the transient vascular benefits of acute exercise alone. Finally, increases in retrograde shear rate promoted by cuff inflation over 50 mmHg seem to provoke a dose-dependent decline in endothelium-mediated vasodilation, at least in young individuals.

It is widely accepted that exercise-induced increases in arterial blood flow and shear stress play an important role in vascular health.[16,29] Exercise is a key factor for NO release

TABLE 1. Summary of studies included in the systematic review.

Study	Subjects	Sample size	Age (years)	Type of exercise or experimental protocol	Exercise intensity	Cuff pressure level (mmHg)	Cuff pressure duration (min)	Cuff placement	Reference artery	Measures of endothelial function	Outcomes
Tinken et al.[27]	Young men, recreationally active	10	28 ± 7	Dynamic handgrip exercise with cuffed and non-cuffed arm	1-2 kg	60	30	Forearm	Brachial artery	Pre- and post-exercise	Non-cuffed arm: ↑ FMD Cuffed arm: ↔ FMD
Paiva et al.[17]	Young men, recreationally active	9	28 ± 5.8	Dynamic handgrip exercise with (EXP arm) and without BFR (CON arm)	60% of MVC	80	20	Forearm	Brachial artery	Baseline, 15, and 60 min after exercise	CON arm: 15 min ↑ FMD EXP arm: 15 and 60 min ↔ FMD
Thijssen et al.[9]	Young men, recreationally active	10	24 ± 3	Cuff intervention (25, 50, or 75 mmHg) vs non-cuffed arm	-	25, 50, 75	30	Forearm	Brachial artery	Baseline and after each intervention	Non-cuffed arm: ↔ FMD Cuffed arm 25 mm Hg: ↔ FMD 50 and 75 mm Hg: ↓ FMD
Schreuder et al.[6]	Young men, recreationally active	13	24 ± 3	Randomized cuff intervention (0, 30, 60 mmHg)	-	0, 30, 60	30	Forearm or thigh	Brachial artery, superficial femoral artery	Baseline and after each intervention	0 and 30 mm Hg: ↔ FMD 60 mmHg: ↓ FMD
Schreuder et al.[7]	Older men, recreationally active	15	68 ± 9	Cuff intervention (0, 30, 60 mmHg)	-	0, 30, 60	30	Forearm or thigh	Brachial artery, superficial femoral artery	Baseline and after each intervention	↔ FMD for all conditions
Dawson et al.[28]	Young men	25	27 ± 4	Cuff placed on the forearm or upper arm (distal or proximal) (60 and 0 mmHg)	-	60	30	Forearm or upper arm	Brachial artery	Baseline and after each intervention	0 mm Hg: ↔ FMD Distal cuff: ↓ FMD Proximal cuff: ↑ FMD

FMD: flow-mediated dilatation; EXP: experimental; CON: control; MVC: maximum voluntary contraction; ↑: increased; ↔: maintained; ↓: decreased.

from the endothelium. In addition to its vasodilator effects, NO is a potent mediator inhibiting vascular smooth muscle contraction, platelet aggregation, and leukocyte adhesion.[30] Several previous studies reported increases in brachial artery FMD following acute and chronic exercise.[31-33] Exercise training is known to improve peripheral vascular function and structure (reflected by increased FMD),[16] inducing clinically relevant benefits for different populations.[34-36]

Cuff inflation appears to promote modifications in brachial artery shear stress and oscillatory flow patterns, reducing the antegrade/retrograde ratio in the experimental exercised arm and impairing the exercise-related benefits. Acute studies showed that FMD increased immediately and 15 min after exercise in the non-cuffed arm, with no changes in the cuffed arm.[17,27] In addition, at least one trial showed that endothelium-independent vasodilation in the brachial artery followed by the administration of sublingual glyceryl trinitrate remained unaffected after exercise performed with and without cuff inflation.[14] These results reinforce that the manipulation of antegrade/retrograde flow during a single session of exercise can result in distinct responses in vascular function and that intraluminal shear stress stimulates NO-mediated endothelium-dependent dilation, not affecting the smooth muscle response reflected by endothelium-independent vasodilatation.

Physiological mechanisms underlying vascular damage or dysfunction are complex. Hemodynamic changes, greater sympathetic activity, increase in oxidative stress/inflammation, or dysfunction of vascular smooth muscle cells[37-40] are possible explanations for FMD decrease and require more detailed investigation. It is important to consider that the time points of post-exercise measurements in presently reviewed studies (immediate, 15 min, and 30 min after exercise)[17,27] do not assess a possible biphasic change in FMD and, therefore, a transient exercise-related decrease in vasodilation.[30] Although the application of moderate restrictive pressure in association with low loads may induce considerable hypertrophy and strength gain,[41] the potential occurrence of negative effects on endothelial function[14,17,24,27] should be considered when prescribing this training method.

In experimental protocols without exercise, cuff pressures ≥ 50 mmHg increased the retrograde shear rate, impairing endothelial function in young subjects,[6,9,30] but FMD decreases were not detected in a single trial including older individuals.[7] Albeit limited, this evidence is suggestive of an age-dependent response of endothelial function to similar arterial hemodynamic occlusion forces. Oscillatory shear stress patterns can induce a pro-atherogenic vascular phenotype.[42] Previous studies demonstrated a reduction in endothelial NO synthase (eNOS) expression[43] and an increased expression of adhesion molecules,[44] inflammatory mediators,[42] endothelin-1,[43] and oxidative stress[45] as a consequence of increased shear stress. Moreover, the retrograde blood flow has been associated with a greater release of cellular markers of endothelial activation or apoptosis,[4] reinforcing its relationship with endothelial dysfunction.

The absence of endothelial function impairment in older subjects after restrictive pressures could be related to an attenuated ability to adapt in response to shear rate resulting in a priori lower FMD. Decreased NO bioavailability contributes to lower endothelium-dependent vasodilation among older individuals.[46] In addition, reduced vascular smooth muscle responsiveness,[47] increased arterial stiffness,[48] and/or hyperactive sympathetic system[49] may be associated with these findings. Finally, the magnitude or duration of the retrograde shear stimulus was insufficient to compromise endothelial function in that specific older sample.[4] Additional research is needed to clarify the underlying physiological mechanisms associated with the lower responsiveness to retrograde shear induced by BFR observed in older individuals when compared to younger ones.

Limitations and practical implications

Some limitations of current research investigating the acute effects of BFR exercise on endothelial function in healthy individuals should be acknowledged. Firstly, the trials included mostly healthy young men, while factors such as age and sex-related hormonal variations and cardiometabolic diseases may influence endothelial function.[50,51] However, this seems to reflect a limitation of the current literature rather than one of the present review. In addition, albeit limited, the studies investigating the impact of BFR on endothelial function are heterogeneous regarding methodology (intensity of exercise, cuff placement site, reference artery, and assessments), which precluded further inferences about the determinants of changes in FMD. Trials applying multiple post-exercise measurements are warranted for determining whether a biphasic and transient decrease in vascular function occurs in different age groups and clinical populations subject to BFR with and without exercise.

The major limitation of our study is the small number of trials included, especially when we consider the number of studies of older adults (only one). In addition, those studies included small sample sizes (82 individuals) and showed moderate methodological quality (6 in the PEDro scale for all studies). This occurred especially in relation to the absence of group randomization and blinding of participants or researchers to the blood restriction or exercise interventions. However, this is not feasible because of the type of intervention.

With regard to practical implications, the result of the systematic review suggests that the increasing levels of BFR appear to attenuate the vascular benefits promoted by physical exercise in young but not in older adults. Although additional studies are needed to determine acute safety, our results suggest that older adults may benefit from BFR training to improve muscle mass and strength as well as physical capacity while preserving vascular health.

CONCLUSION

The available evidence suggests that an exercise-related increase in shear stress leads to greater NO release and FMD. The addition of BFR appears to attenuate this response. A dose-response relationship between retrograde blood flow elicited by BFR and reduction in endothelial function seems to occur in healthy and recreationally active young subjects, but not in older individuals. Future research needs to elucidate the determinants of FMD changes associated with exercise (type, duration, and intensity) and BFR (magnitude and duration) in different clinical populations as well as the potentially involved underlying mechanisms.

Conflict of interest

The authors declare no conflicts of interest.

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Authors' contribution

GGC: data curation, formal analysis, investigation, methodology, software, validation, visualization, writing – original draft, writing – review & editing. KGL: conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, supervision, validation, visualization, writing – original draft, writing – review & editing. DAB: visualization, writing – original draft, writing – review & editing. MGCS: visualization, writing – original draft, writing – review & editing. EB: visualization, writing – review & editing. PF: methodology, validation, visualization, writing – original draft, writing – review & editing. RBO: conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, supervision, validation, visualization, writing – original draft, writing – review & editing.

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