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What is New on the Link Between Obstructive Sleep Apnea, Dysmetabolism and Cardiovascular Diseases

Factos Novos sobre a Ligação Entre Apneia Obstrutiva do Sono, Dismetabolismo e Doenças Cardiovasculares

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Abstract

Obstructive sleep apnea (OSA), characterized by recurrent airflow cessation during sleep, affects nearly 1 billion adults worldwide and is associated with various comorbidities, including metabolic disorders and cardiovascular diseases (CVD). Indeed, novel research findings highlight the complex interplay between OSA, dysmetabolism, and CVD. In this work, we briefly discuss mechanistic insights into OSA-related metabolic dysregulation, such as chronic intermittent hypoxia (CIH) and sleep fragmentation (SF). We particularly focus on pathways involving sympathetic activation, neuroendocrine dysregulation, mitochondrial dysfunction, oxidative stress, inflammation, and gut microbiota alterations. Emerging concepts, including epigenetic modifications and extracellular vesicle-mediated signaling, which provide novel avenues for understanding OSA pathophysiology and for identifying therapeutic targets will also be discussed. It is pivotal to identify biomarkers and predictive parameters that offer potential for risk stratification, early diagnosis, and treatment optimization in OSA patients. Additionally, interdisciplinary collaboration among healthcare professionals enables the development of comprehensive intervention strategies encompassing continuous positive airway pressure (CPAP) therapy, oral appliance optimization, cardiovascular risk assessment, lifestyle interventions, smoking cessation programs, and pharmacotherapy optimization. These collaborative efforts aim to mitigate CVD risk and improve clinical outcomes, emphasizing personalized, patient-centered care to address the multifaceted challenges posed by OSA and metabolic disorders.

Keywords: obstructive sleep apnea; metabolic disorders; cardiovascular diseases; comprehensive intervention strategies

Resumo

A apneia obstrutiva do sono (AOS), caracterizada pela cessação recorrente do fluxo aéreo durante o sono, afeta quase mil milhões de adultos em todo o mundo e está associada a diversas comorbidades, incluindo distúrbios metabólicos e doença cardiovascular (DCV). Na verdade, novas descobertas destacam a complexa interação entre AOS, dismetabolismo e DCV. Neste trabalho discutimos brevemente os mecanismos sobre a desregulação metabólica relacionada com AOS, como a hipóxia crónica intermitente (HCI) e a fragmentação do sono (FS). Iremos concentrar-nos particularmente nas vias que envolvem a ativação simpática, desregulação neuroendócrina, disfunção mitocondrial, stress oxidativo, inflamação e alterações da microbiota intestinal. Conceitos emergentes, incluindo modificações epigenéticas e sinalização mediada por vesículas extracelulares, que fornecem novos caminhos para a compreensão da fisiopatologia da AOS e para a identificação de alvos terapêuticos também serão discutidos. É fundamental identificar biomarcadores e parâmetros preditivos que ofereçam potencial para estratificação de risco, diagnóstico precoce e otimização do tratamento em pacientes com AOS. Além disso, a colaboração interdisciplinar entre profissionais de saúde permite o desenvolvimento de estratégias de intervenção abrangentes que incluem terapia de Pressão Positiva Contínua nas Vias Aéreas (CPAP), otimização de aparelhos orais, avaliação de risco cardiovascular, intervenções no estilo de vida, programas de cessação do tabagismo e otimização da farmacoterapia. Estes esforços colaborativos visam mitigar o risco de DCV e melhorar os resultados clínicos, enfatizando cuidados personalizados e centrados no paciente para enfrentar os desafios multifacetados colocados pela AOS e disfunções cardiometabólicas.

Palavras-chave: apneia obstrutiva do sono; distúrbios metabólicos; doença cardiovascular; estratégias de intervenção abrangentes

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> INTRODUCTION

According to the American Academy of Sleep Medicine, sleep-related breathing disorders encompass a spectrum of conditions characterized by irregularities in respiration during sleep. [1] These disorders are categorized into four main classes: obstructive sleep apnea (OSA) syndromes, sleep-related hypoventilation disorders, central apnea syndromes, and sleep-related hypoxemia disorder. [2] Among these, OSA stands as the most prevalent, affecting nearly 1 billion adults aged 30–69, with a higher incidence among men. OSA is typified by recurrent episodes of partial (hypoapnea) or complete (apnea) cessation of airflow due to the collapse of the pharyngeal airway during sleep. [1] These occurrences lead to diminished oxygen levels and increased carbon dioxide levels, triggering chemoreceptor activation and sympathetic nervous system (SNS) response to restore oxygenation. [3] The consequent chronic intermittent hypoxia (CIH) resulting from these cyclic events, along with associated sleep fragmentation (SF), contribute to the pathophysiology of OSA.

Over time, extensive research has revealed a strong correlation between OSA and various comorbidities, including cardiovascular disease, metabolic disorders, neurological conditions, and pulmonary ailments. Notably, OSA has been linked to metabolic dysregulation, manifesting in obesity, metabolic syndrome (MetS), and type 2 diabetes (T2D). [4] Indeed, MetS is highly prevalent among OSA patients, with rates reaching up to 80%, while at least 50% of T2D cases are associated with OSA, irrespective of obesity status. [5,6] Furthermore, the severity of OSA positively correlates with insulin resistance and glucose intolerance, marking OSA as an independent risk factor for T2D. [5,7] Conversely, T2D also heighs the risk of developing OSA, establishing a bidirectional relationship between the two conditions. [4]

The mechanistic underpinnings linking CIH and SF in OSA to MetS and its core components remain under investigation, although various pathophysiological mechanisms have been proposed. These mechanisms include heighened sympathetic activation, hypothalamus-pituitary axis dysregulation, alterations in adipokine levels, mitochondrial dysfunction, oxidative stress, inflammation, and modulation of genes involved in lipogenesis, among others. [4,7-9] Recent research has explored adipose tissue dysfunction as a potential driver of metabolic dysfunction in CIH, revealing early-stage metabolic alterations characterized by hyperinsulinemia and whole-body insulin resistance, despite the absence of significant changes in adipocyte morphology, tissue oxygenation, angiogenesis, oxidative stress, or metabolism. [10,11] In addition to MetS, non-alcoholic fatty liver disease (NAFLD) represents another disorder commonly associated with metabolic dysfunction. NAFLD, affecting approximately 30% of adults and exhibiting a higher prevalence in men, is influenced by factors such as age and the presence of comorbidities like OSA. [12] Overall, the intricate interplay between CIH in OSA and metabolic dysregulation underscores the importance of understanding the underlying mechanisms to develop targeted therapeutic interventions and mitigate the associated health risks.

While the main mechanisms connecting OSA, dysmetabolism, and cardiovascular diseases (CVD) have been largely established, ongoing research endeavors are shedding light on novel insights and refining our comprehension of the intricate interplay among these conditions. Here, we delve into potential new mechanisms and emerging concepts that researchers may be exploring (Figure 1).

> EMERGING MECHANISMS LINKING OSA, DYSMETABOLISM AND CVD

The hypothalamus orchestrates energy balance, appetite control, and glucose metabolism through intricate neural circuits and neuropeptide signaling pathways. Emerging evidence suggests that OSA-induced alterations in hypothalamic function, including disruptions in orexigenic and anorexigenic signaling pathways, may contribute to dysregulated energy intake, impaired glucose tolerance, and dyslipidemia. [13] Understanding the neurobiological mechanisms linking OSA to hypothalamic dysfunction and metabolic dysregulation offers opportunities for targeted interventions aimed at restoring metabolic homeostasis and preventing cardiovascular complications. Furthermore, dysregulation of neuroendocrine axes, including the hypothalamic-pituitary-adrenal (HPA) axis and the SNS, contributes to the pathogenesis of metabolic disorders and cardiovascular complications. [14,15] CIH in OSA disrupts neuroendocrine balance, leading to hyperactivation of the HPA axis, increased sympathetic tone, and dysregulated release of catecholamines and cortisol. [16] These hormonal alterations promote insulin resistance, dyslipidemia, hypertension, and endothelial dysfunction, exacerbating the risk of CVD. [15,17]

Mitochondrial dysfunction and oxidative stress also represent key pathophysiological mechanisms underlying OSA-associated metabolic alterations and cardiovascular injury. [18] Intermittent hypoxia-reoxygenation cycles during apneic events disrupt mitochondrial bioenergetics, impair antioxidant defenses, and promote reactive

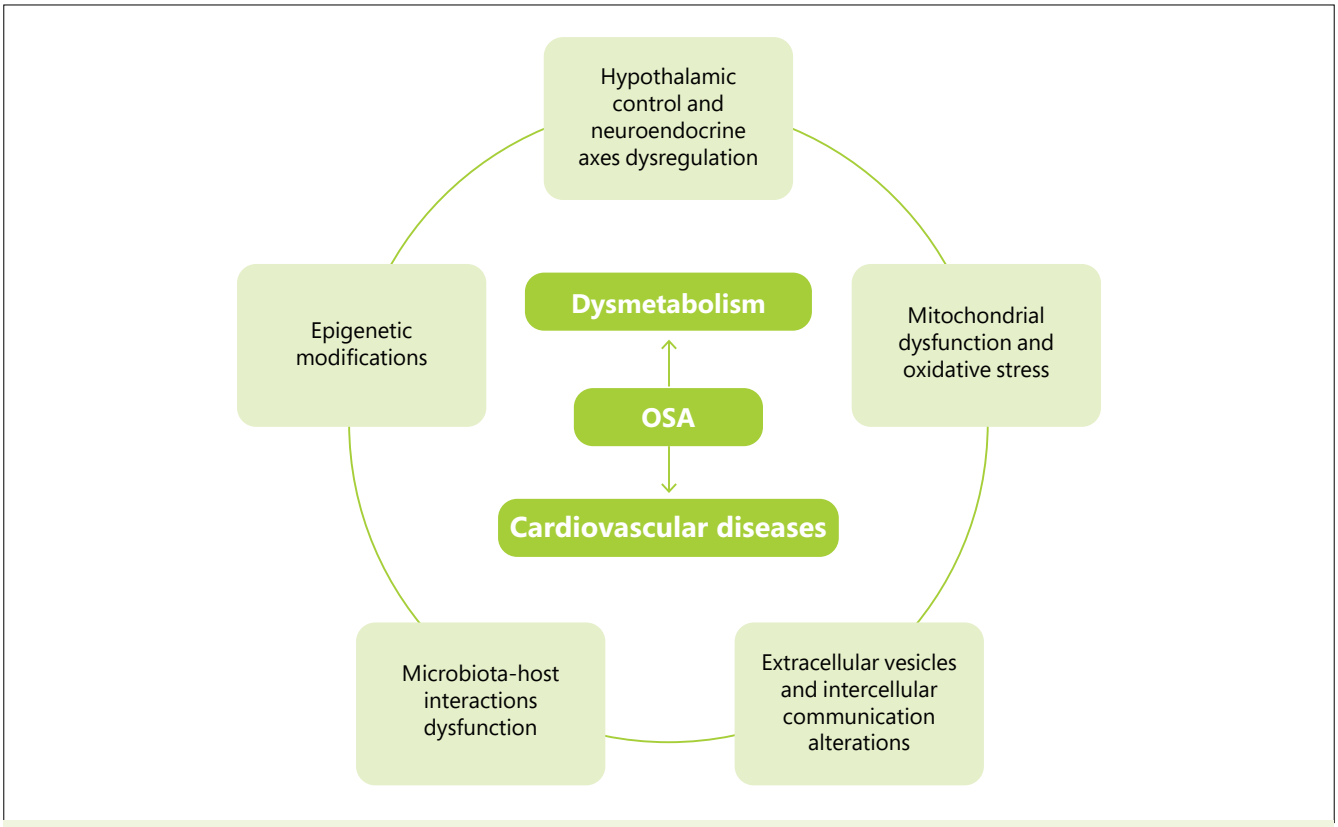

Figure 1 - Mechanisms and emerging concepts connecting OSA-dysmetabolism-CVD to be explored by researchers to identify new markers and therapeutic targets to treat these pathologies.

oxygen species (ROS) generation. Excessive ROS production triggers inflammation, endothelial dysfunction, and oxidative damage, promote a proatherogenic environment. [19] Novel therapeutic interventions targeting mitochondrial protection, antioxidant supplementation, or ROS scavenging may attenuate OSA-induced metabolic disturbances and cardiovascular risk.

Notably, extracellular vesicles, such as exosomes and microvesicles, are vital mediators of intercellular communication by ferrying bioactive molecules between cells and tissues. Studies exploring the role of extracellular vesicles derived from adipose tissue, endothelial cells, and immune cells in OSA-associated metabolic dysfunction and vascular injury may unveil novel signaling pathways implicated in cardiovascular pathology. [20-22] Additionally, investigations into the cargo of circulating extracellular vesicles as potential biomarkers of OSA severity and cardiovascular risk hold promise for non-invasive risk stratification and disease monitoring. [23,24]

Recent studies have also unveiled the pivotal role of the gut microbiota in influencing metabolic and cardiovascular health. [25] Dysbiosis, characterized by imbalances in gut bacteria composition and function, has been implicated in insulin resistance, inflammation, and atherosclerosis. Research into the interplay between OSA--induced hypoxia, gut microbiota dysregulation, and metabolic dysfunction offers promising avenues for understanding the systemic impact of sleep-disordered breathing on cardiovascular outcomes. [26-28]

Finally, epigenetic mechanisms, encompassing DNA methylation, histone modifications, and non-coding RNA regulation, play a crucial role in gene expression regulation and phenotypic adaptation. Emerging evidence suggests that OSA-related hypoxia and oxidative stress may induce epigenetic alterations, thereby modulating the expression of genes involved in glucose metabolism, lipid homeostasis, and vascular function. [29-31] Therefore, understanding the epigenetic signatures associated with OSA, dysmetabolism, and CVD could provide mechanistic insights and identify potential therapeutic targets.

These emerging concepts underscore the dynamic nature of research in elucidating the mechanistic underpinnings of the link between OSA, dysmetabolism, and CVD. Future research into these novel pathways and therapeutic targets holds promise for developing inno-

vative strategies to mitigate cardiovascular risk and improve clinical outcomes in individuals with sleep-disordered breathing and metabolic disorders.

> MARKERS AND PARAMETERS RELATED WITH OSA-DYSMETABOLISM-CVD LINK

In recent years, advancements in clinical studies, biomarker research, and predictive parameters have offered new avenues for understanding the intricate connections between OSA, dysmetabolism, and CVD. Here, we discuss emerging markers and parameters that can define risk assessment, early diagnosis, and treatment strategies.

Current research led to crucial advancements in the attempt to identify biomarkers that can serve as indicators of OSA severity, metabolic dysfunction, and cardiovascular risk (Table 1).

Studies exploring the association between circulating inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), with OSA severity and cardiovascular outcomes opens the path for risk stratification and personalized treatment approaches. Systemic inflammation is a key player in the pathogenesis of OSA, dysmetabolism, and CVD. [32,33] Thus, these biomarkers, and soluble adhesion molecules show promise in predicting cardiovascular risk and metabolic complications in individuals with OSA.

Endothelial dysfunction precedes the development of CVD and may be assessed through biomarkers like endothelin-1 (ET-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1). These markers help identify individuals at higher risk of cardiovascular events in the context of OSA. Furthermore, certain genetic variants predispose individuals to OSA and cardiovascular risk. [33,34]

Biomarkers such as single nucleotide polymorphisms (SNPs) in genes related to airway anatomy and vascular function provide insights into genetic susceptibility and personalized management strategies. Many studies have used Mendelian randomization (MR) approach to explore the potential causal association between OSA with CVD in the general population. [35,36]

As OSA is associated with cardiac abnormalities, it may be detected through biomarkers like N-terminal pro-B--type natriuretic peptide (NT-proBNP) and troponins. Monitoring changes in cardiac biomarkers aids in the early detection of subclinical cardiac dysfunction in OSA patients. [37,38] In addition, objective measurements obtained during sleep studies, such as apnea-hypopnea index (AHI) and oxygen desaturation index (ODI), serve as important predictors of OSA severity and cardiovascular outcomes. Integrating these parameters with biomarker profiling enhances risk assessment in OSA patients.

Another set of possible markers associated with metabolism must be highlighted. Dysregulation of glucose and lipid metabolism is common in OSA and is associated with increased cardiovascular risk. [5,39] Thus, fasting glucose, insulin, adipokines, and lipid profiles provide insights into metabolic disturbances and cardiovascular outcomes in individuals with OSA thus highlighting the possibility to encounter relevant markers in those pathways.

Intermittent hypoxia in OSA leads to increased ROS, contributing to endothelial dysfunction and vascular injury. Biomarkers such as malondialdehyde (MDA) and oxidized low-density lipoprotein (LDL) reflect oxidative damage and may serve as indicators of cardiovascular risk in OSA patients. [40-42] However, some discrepancies have been found on these associations.

Notably, omics technologies enable the discovery of no-

Table I - Emerging biomarkers that can serve as indicators of OSA severity, metabolic dysfunction and cardiovascular risk.

Emerging biomarkers indicators of OSA-dysmetabolism-CVD link	Examples
Inflamatory markers	C-RP, IL6, TNFα, etc.
Endothelial function markers	ET-1, vWF, sVCAM-1, etc.
Genetic markers	SNPs on genes related to airway anatomy, inflammation, etc.
Cardiac biomarkers	NT-proBNP, troponins, BNP, etc.
Metabolic biomarkers	Fasting glucose, HbA1c, insulin, etc.
Oxidative stress markers	MDA, 8-isoprostane, LDL, SOD, catalase, etc.
Multi-omics derived data	Data from genomics, transcriptomics, metabolomics, etc.

C-RP: C-reactive protein; IL6: interleukin-6; TNFα: tumor necrosis factor alpha; ET-1: endothelin-1; vWF: von Willebrand factor; sVCAM-1: soluble vascular cell adhesion molecule-1; SNPs: single nucleotide polymorphisms; NT-proBNP: N-terminal pro-B-type natriuretic peptide; BNP: brain natriuretic peptide; HbA1c: glycated hemoglobin; MDA: malondialdehyde; LDL: low-density lipoprotein; SOD: superoxide dismutase.

vel biomarkers associated with OSA pathophysiology and cardiovascular risk. [43] Integration of multi-omics data, genomics, transcriptomics, proteomics, metabolomics and microbiomics, may unveil new diagnostic and therapeutic targets for personalized medicine approaches in OSA patients. [44] By exploring these biomarkers and predictive parameters, clinicians can enhance risk assessment, tailor treatment strategies, and improve outcomes for individuals with sleep-disordered breathing and metabolic disorders.

> INTERVENTION STRATEGIES

Interdisciplinary collaboration among sleep medicine specialists, endocrinologists, cardiologists, and nutritionists holds promise in developing innovative intervention strategies to address the complex interplay between OSA-dysmetabolism-CVD. These collaborative efforts can lead to the design and implementation of comprehensive, patient-centered approaches that target multiple aspects of health simultaneously. Herein, we will discuss potential intervention strategies to battle these intricate pathologies. It is to our knowledge that CPAP therapy remains a cornerstone in managing moderate to severe OSA, [45,46] even when linked with CVD. However, its effect on blood pressure (BP) and other cardiovascular parameters has been challenging. [47] Therefore, collaborative efforts can focus on enhancing patient education, improving device comfort, and addressing barriers to adherence. [48] Additionally, close monitoring of CPAP efficacy on metabolic parameters and cardiovascular risk factors can guide treatment optimization. Multidisciplinary teams can also conduct thorough cardiovascular risk assessments, integrating traditional clinical parameters with novel biomarkers and imaging modalities. Collaborative care plans can then be tailored to address individual risk profiles, incorporating pharmacological and lifestyle interventions to mitigate cardiovascular risk in OSA patients. In consonance, psychologists, sleep specialists, and cardiologists can collaborate to integrate stress reduction techniques into OSA management protocols. Research initiatives may investigate the effects of mindfulness-based interventions, relaxation therapies, and stress management programs on sleep quality, metabolic parameters, and cardiovascular outcomes.

Oral appliances, such as mandibular advancement devices (MADs) or tongue-retaining devices (TRDs), are alternative treatment options for mild to moderate OSA or CPAP-intolerant individuals. These devices reposition the jaw or tongue to prevent airway collapse during sleep, improving airflow and reducing snoring and sleep apnea events. While less effective than CPAP in lowering AHI, oral appliance therapy may still confer benefits in terms of daytime symptoms, quality of life, and possibly cardiovascular risk. [49]

There are also lifestyle interventions that can be followed. Nutritionists and sleep specialists can work together to develop dietary interventions targeting OSA-associated metabolic dysfunction and cardiovascular risk factors. [50] Collaboration may involve implementing personalized nutrition plans, monitoring dietary adherence, and assessing the impact of dietary changes on OSA severity and cardiometabolic health. Furthermore, multidisciplinary weight management programs, integrating dietary counseling, exercise prescriptions, and behavioral therapies, can be tailored to address the unique needs of OSA patients with metabolic comorbidities. Additionally, exercise specialists and sleep medicine experts can collaborate to develop exercise interventions tailored to OSA patients, considering their sleep-related symptoms and cardiovascular risk factors. [51] Research endeavors may explore the effects of different exercise modalities on sleep quality, metabolic health, and cardiovascular outcomes in this population. In fact, some studies have shown that exercise can be the second most effective treatment for OSA behind CPAP in terms of reducing AHI in people with diagnosed OSA. [52] Another relevant issue is possible joint efforts between pulmonologists, sleep specialists, and behavioral therapists that can enhance smoking cessation interventions for OSA patients, considering their unique respiratory challenges and cardiovascular risks. This intervention can benefit OSA patients and CVD risk by different mechanism: decrease of upper airway inflammation, normalization of sleep architecture, reduction of arousals events, etc. [53] Finally, collaboration between endocrinologists, cardiologists, and sleep specialists can optimize pharmacotherapy for OSA-associated metabolic dysregulation and CVD. The main targets for the current available pharmacotherapy are based on 1) pharyngeal motor effectors; 2) upper airway sensory afferents mediating reflex pharyngeal dilator muscle responses to sub-atmospheric airway collapsing pressures; 3) chemosensory afferents and ventilatory control system; and 4) sleep-wake mechanisms. [54] However, research efforts may focus on identifying novel pharmacological targets and assessing the efficacy of combination therapies in improving cardiometabolic outcomes in OSA patients. Integrated care models, involving coordinated care delivery among various healthcare providers, can optimize OSA management and cardiometabolic risk reduction.

By promoting interdisciplinary collaboration and leveraging the expertise of diverse healthcare professionals, innovative intervention strategies can be developed to address the multifaceted challenges posed by the link between OSA-dysmetabolism-CVD. These collaborative efforts hold the potential to improve patient outcomes, enhance quality of life, and reduce the global burden of cardiovascular morbidity and mortality associated with sleep-disordered breathing and metabolic disorders.

> CONCLUSIONS

In conclusion, the intricate relationship between OSA, dysmetabolism, and CVD underscores the multifaceted nature of these interconnected health conditions. Extensive research has elucidated the complex pathophysiological mechanisms linking OSA to metabolic dysfunction and cardiovascular complications, shedding light on novel insights and emerging concepts. As we aim to deepen our understanding of these interrelationships, it becomes increasingly evident that interdisciplinary collaboration is paramount in developing innovative intervention strategies to address the holistic needs of individuals affected by these conditions. The collaboration among sleep medicine specialists, endocrinologists, cardiologists, and nutritionists holds promise in designing and implementing comprehensive, patient-centered approaches that target various aspects of health simultaneously. Through collaborative efforts, interventions such as CPAP therapy, cardiovascular risk assessments, stress reduction techniques, dietary interventions, weight management programs, smoking cessation interventions, and pharmacotherapy optimization can be tailored to meet the unique needs of OSA patients with cardiometabolic comorbidities. Furthermore, ongoing research endeavors exploring novel mechanisms, biomarkers, and therapeutic targets continue to expand our knowledge base and refine our treatment approaches. From unraveling the neurobiological underpinnings of hypothalamic dysfunction to investigating the role of gut microbiota and epigenetic mechanisms, these advancements pave the way for personalized medicine approaches and targeted interventions aimed at mitigating cardiovascular risk and improving clinical outcomes. In essence, the journey towards improving patient outcomes, enhancing quality of life, and reducing the global burden of cardiovascular morbidity and mortality associated with sleep-disordered breathing and metabolic disorders requires collective efforts, unwavering dedication, and a steadfast commitment to advancing knowledge and innovation in the field. <

Conflicts of interests/*Conflitos de interesses*:
The authors declare that they have no conflicts of interests./*Os autores declaram a inexistência de conflitos de interesses.*

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