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HERPES ZOSTER AND CARDIOVASCULAR RISK: CURRENT EVIDENCE AND CLINICAL PERSPECTIVES

Herpes Zoster e Risco Cardiovascular: Evidências Atuais e Perspectivas Clínicas.

Herpes Zóster y Riesgo Cardiovascular: Evidencias Actuales y Perspectivas Clínicas

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ABSTRACT

Herpes zoster results from the reactivation of latent varicella-zoster virus in sensory ganglia and is more prevalent among older adults and immunocompromised individuals. Recent evidence has demonstrated an association between herpes zoster infection and an increased risk of cardiovascular events, which remains underrecognized in clinical practice. To analyze current scientific evidence regarding the relationship between herpes zoster and cardiovascular risk, with emphasis on the main associated events and clinical implications. This is an integrative literature review conducted through searches in the PubMed, Scopus, and Web of Science databases, including studies published in recent years. Observational studies, cohort studies, and systematic reviews evaluating the association between herpes zoster, vaccination, antiviral treatment, and cardiovascular events were included. Duplicate articles, case reports, and studies lacking relevant clinical data were excluded. The analyzed studies demonstrated a significant increase in the risk of cardiovascular events, particularly stroke, transient ischemic attack, acute myocardial infarction, and coronary artery disease, especially within the first year after viral reactivation. Herpes zoster ophthalmicus showed an even stronger association with these outcomes. Additionally, evidence indicates that herpes zoster vaccination is associated with a reduced risk of stroke, whereas antiviral treatment did not consistently demonstrate a statistically significant reduction in this risk. Herpes zoster infection is associated with an increased cardiovascular risk, highlighting the need for greater clinical surveillance, particularly in the post-infection period. Vaccination emerges as a potentially protective strategy, while the lack of specific guidelines underscores the importance of further research to guide prevention and management of these patients.

Keywords: *Herpes Zoster; Cardiovascular Diseases; Stroke; Vaccination; Varicella-Zoster Virus.*

RESUMO

A herpes zóster resulta da reativação do vírus varicela-zóster latente nos gânglios sensitivos, sendo mais prevalente em idosos e indivíduos imunossuprimidos. Evidências recentes têm demonstrado associação entre a infecção por herpes zóster e o aumento do risco de eventos cardiovasculares, ainda pouco reconhecida na prática clínica. O objetivo foi analisar as evidências científicas atuais sobre a relação entre herpes zóster e risco cardiovascular, com ênfase nos principais eventos associados e nas implicações clínicas. Trata-se de uma revisão integrativa da literatura, realizada por meio de buscas nas bases de dados PubMed, Scopus e Web of Science, abrangendo estudos publicados nos últimos anos. Foram incluídos estudos observacionais, coortes e revisões sistemáticas que avaliaram a associação entre herpes zóster, vacinação, tratamento antiviral e a ocorrência de eventos cardiovasculares. Artigos duplicados, relatos de caso e estudos sem dados clínicos relevantes foram excluídos. Os estudos analisados demonstraram aumento significativo do risco de eventos cardiovasculares, especialmente acidente vascular cerebral, ataque isquêmico transitório, infarto agudo do miocárdio e doença arterial coronariana, principalmente no primeiro ano após a reativação viral. O herpes zóster oftálmico apresentou associação ainda mais forte com esses eventos. Além disso, evidências indicam que a vacinação contra herpes zóster está associada à redução do risco de acidente

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vascular cerebral, enquanto o tratamento antiviral não demonstrou redução estatisticamente significativa desse risco de forma consistente. A infecção por herpes zóster está associada a um aumento do risco cardiovascular, ressaltando a necessidade de maior vigilância clínica, especialmente no período pós-infecção. A vacinação surge como estratégia potencialmente protetora, enquanto a ausência de diretrizes específicas reforça a importância de novas pesquisas para orientar a prevenção e o manejo desses pacientes.

Palavras-chave: Herpes Zoster; Doenças Cardiovasculares; Acidente Vascular Cerebral; Vacinação; Vírus Varicela-Zóster.

RESUMEN

Sensitivos y es más prevalente en adultos mayores e individuos inmunocomprometidos. Evidencias recientes han demostrado una asociación entre la infección por herpes zóster y un mayor riesgo de eventos cardiovasculares, aún poco reconocida en la práctica clínica. Analizar las evidencias científicas actuales sobre la relación entre el herpes zóster y el riesgo cardiovascular, con énfasis en los principales eventos asociados y sus implicaciones clínicas. Se trata de una revisión integradora de la literatura realizada mediante búsquedas en las bases de datos PubMed, Scopus y Web of Science, incluyendo estudios publicados en los últimos años. Se incluyeron estudios observacionales, estudios de cohorte y revisiones sistemáticas que evaluaron la asociación entre herpes zóster, vacunación, tratamiento antiviral y la ocurrencia de eventos cardiovasculares. Se excluyeron artículos duplicados, reportes de casos y estudios sin datos clínicos relevantes. Los estudios analizados demostraron un aumento significativo del riesgo de eventos cardiovasculares, especialmente accidente cerebrovascular, ataque isquémico transitorio, infarto agudo de miocardio y enfermedad arterial coronaria, principalmente durante el primer año posterior a la reactivación viral. El herpes zóster oftálmico mostró una asociación aún más fuerte con estos eventos. Además, las evidencias indican que la vacunación contra el herpes zóster se asocia con una reducción del riesgo de accidente cerebrovascular, mientras que el tratamiento antiviral no mostró de forma consistente una reducción estadísticamente significativa de dicho riesgo. La infección por herpes zóster se asocia con un aumento del riesgo cardiovascular, lo que resalta la necesidad de una mayor vigilancia clínica, especialmente en el período posterior a la infección. La vacunación surge como una estrategia potencialmente protectora, mientras que la ausencia de directrices específicas refuerza la importancia de nuevas investigaciones para orientar la prevención y el manejo de estos pacientes.

Palabras clave: *Herpes Zóster; Enfermedades Cardiovasculares; Accidente Cerebrovascular; Vacunación; Virus Varicela-Zóster.*

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1. INTRODUCTION

Herpes zoster is a viral disease related to the reactivation of the Varicella–Zoster Virus (VZV), which is the same etiologic agent responsible for varicella, commonly known as chickenpox. After the primary infection, which usually occurs during childhood, VZV remains latent in the dorsal root ganglia of sensory nerves. Viral reactivation may occur decades after the initial infection, particularly in immunosuppressive contexts such as aging. From an epidemiological perspective, the incidence of herpes zoster varies according to age: among healthy adults, it is estimated to range from 1.2 to 3.4 cases per 1,000 person-years, whereas in individuals over 65 years of age, the incidence increases to approximately 3.9–11.8 cases per 1,000 person-years.

Neurological involvement related to VZV reactivation may occur, characterized by inflammation of the dorsal root ganglia and, more rarely, the ventral roots and meninges, which explains the characteristic neuritic pain associated with herpes zoster. Among neurological complications, postherpetic neuralgia is the most common, defined as persistent pain following the resolution of cutaneous lesions.

Beyond neurological manifestations, several prominent studies have demonstrated an association between herpes zoster infection and an increased risk of multiple cardiovascular events in both the short and long term, with particular relevance in younger patients. The main cardiovascular events associated with VZV reactivation include transient ischemic attack, myocardial infarction, and coronary artery disease. These studies report a stronger association with herpes zoster ophthalmicus (HZO), with cardiovascular events occurring predominantly within one year after viral reactivation and exhibiting even higher incidence rates.

Observational studies have also investigated the influence of herpes zoster vaccination and antiviral therapy on the risk of stroke following herpes zoster. Vaccination against herpes zoster has been associated with a reduced risk of stroke, suggesting a potential protective effect. In contrast, antiviral treatment, such as acyclovir, did not demonstrate a statistically significant association with stroke risk reduction in the analyzed studies.

Considering these findings, the present study reinforces the clinical perspective that the underestimation of post–herpes zoster cardiovascular risk is not only related to insufficient surveillance, but also to the lack of well-defined clinical guidelines addressing cardiovascular monitoring and prevention following VZV reactivation.

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2. METHODOLOGY

This integrative literature review was conducted through searches in the PubMed, Scopus, and Web of Science databases, encompassing studies published in recent years. Observational studies, cohort studies, and systematic reviews evaluating the association between herpes zoster, vaccination, antiviral treatment, and the occurrence of cardiovascular events were included. Duplicate articles, case reports, and studies lacking relevant clinical data were excluded.

3. DEVELOPMENT

The association between varicella-zoster virus (VZV) reactivation and cardiovascular events is based on multiple pathophysiological mechanisms that begin after primary infection, with viral latency persisting in neural ganglia, particularly sensory and autonomic ganglia. In the context of immunosuppression or aging, the virus may reactivate and travel along nerve fibers, reaching arteries through the adventitial layer, especially in cranial regions. Once the vascular wall is reached, VZV infects cells in the adventitia, progressively spreading to the media and intima, thereby promoting vascular remodeling.

The virus-induced inflammatory response is central to this process and manifests as follows: after infection, there is an initial recruitment of neutrophils, followed by infiltration of T lymphocytes and macrophages into the adventitial and intimal layers. These cells release soluble factors, such as matrix metalloproteinases, which degrade the extracellular matrix, weaken vascular structure, induce smooth muscle cell death in the media, and contribute to the formation of aneurysms, dissections, or stenoses. In addition, immune dysregulation plays a crucial role, as VZV-infected arteries exhibit reduced expression of regulatory molecules such as PD-L1 (programmed death ligand-1), which may favor persistent vascular inflammation.

VZV reactivation occurs in the dorsal root and trigeminal ganglia, from which the virus is transported via axons to nerve endings that innervate cerebral and extracranial arteries. Once in the arterial wall, VZV initiates productive infection in the adventitia, infecting adventitial fibroblasts, resident macrophages, and endothelial cells of the vasa vasorum, where viral antigens such as gE and IE63 have been detected in immunohistochemical studies.

As the virus progresses to the medial and intimal layers of the arterial wall, vascular smooth muscle cells in the media become infected, while intimal infection exhibits a transmural pattem

confirmed by histopathological analyses. This process is accompanied by marked activation of inflammatory pathways, with intense infiltration of CD4+/CD8+ T lymphocytes, neutrophils, and macrophages, as well as the release of pro-inflammatory cytokines (IL-6, TNF-α, IFN-γ) and activation of metalloproteinases (MMP-3 and MMP-9).

This inflammatory cascade leads to extracellular matrix degradation, loss of smooth muscle cells, and fragmentation of the internal elastic lamina. Consequently, a pattern of necrotizing and proliferative arteritis develops, combined with transmural destruction and intimal hyperplasia, resulting in luminal stenosis or, in some cases, fusiform aneurysms due to wall fragility. This direct invasion of the arterial wall represents a central pathogenic mechanism of VZV infection.

Viral presence and associated inflammation result in significant endothelial dysfunction, characterized by reduced nitric oxide (NO) production and increased expression of pro-thrombotic molecules such as tissue factor, establishing a microenvironment conducive to thrombosis. The combination of luminal stenosis, endothelial injury, and increased thrombogenicity enables the development of acute ischemic events, particularly ischemic stroke, which is the most frequently associated clinical manifestation of VZV vasculopathy. Angiographic and histopathological studies demonstrate that VZV-induced vasculitis may exhibit a multifocal pattern involving both small and large vessels, contributing to cortical, subcortical, or lacunar ischemic lesions, often simultaneously.

Multiple epidemiological studies support the association between herpes zoster (HZ) and an increased risk of cardiovascular events in both the short and long term. A systematic review and meta-analysis of 12 studies involving nearly 7.9 million participants with follow-up periods of up to 28 years evaluated the occurrence of herpes zoster (including ophthalmic zoster) and its association with increased risk of cerebrovascular events (such as stroke and transient ischemic attack) and cardiac events (such as myocardial infarction and coronary artery disease). In the fixed-effects model, the odds ratio (OR) for cerebrovascular events within three months after HZ was approximately 1.34 (95% CI: 1.22–1.46). For herpes zoster ophthalmicus, patients exhibited even higher odds of cerebrovascular events, reaching up to 4.42 within one year, according to fixed-effects analysis. These findings demonstrate that HZ is associated with an increased risk of cerebrovascular and cardiac events.

Other studies using electronic health record databases and self-controlled case series designs have shown a transient increase in stroke risk shortly after an episode of HZ, which tends to attenuate over 6 to 12 months. In particular, herpes zoster ophthalmicus appears to confer a higher stroke risk

than other forms of HZ. Additionally, a prospective cohort study composed of three large cohorts, totaling more than 200,000 participants and over two million person-years of follow-up, found that individuals with a history of HZ had an elevated long-term risk of stroke and coronary heart disease. Notably, stroke risk remained elevated years after the HZ episode: in the group 5–8 years post-HZ, the adjusted hazard ratio (HR) for stroke was 1.38 (95% CI: 1.10–1.74), and between 9–12 years it was 1.28 (95% CI: 1.03–1.59).

Conversely, a retrospective cohort study involving approximately 41,930 patients showed that the risk of major adverse cardiac and cerebrovascular events (MACE) was 19% higher in the first year after HZ diagnosis, adjusted for age, dyslipidemia, hypertension, and other factors. However, this study did not demonstrate a clear long-term protective benefit of antiviral treatment, suggesting that HZ functions not only as a marker but also as a risk factor for cardiovascular disease.

Overall, these epidemiological data are highly relevant, first by recognizing HZ as a cardiovascular risk factor and second by emphasizing the temporal relationship of these risks, which are typically highest in the months following viral reactivation. Moreover, these findings indicate a strong association between HZ vaccination and risk reduction, as vaccination decreases the incidence of postherpetic neuralgia and, consequently, reduces cardiovascular risk.

A particularly relevant study demonstrated that VZV infection of human cerebral vascular cells directly increases the production of pro-inflammatory cytokines, reinforcing the hypothesis that VZV causes vasculopathy and contributes to complications such as stroke or giant cell arteritis. This study utilized primary human cerebral vascular adventitial fibroblasts, perineurial cells, and vascular smooth muscle cells, with fetal lung fibroblasts serving as controls.

These cells were infected with VZV and compared with uninfected controls, and 30 inflammatory cytokines were measured after 72 hours. The main findings showed significant increases in IL-8 across all tested cell types; IL-6 increased in adventitial fibroblasts, perineurial cells, and fetal lung fibroblasts, but not in vascular smooth muscle cells; VEGF-A increased in adventitial fibroblasts, vascular smooth muscle cells, and fetal lung fibroblasts but decreased in perineurial cells. Other cytokines exhibited cell-type-specific alterations.

These findings suggest that direct VZV infection of vascular cells creates a highly pro-inflammatory environment independent of immune cell involvement. Elevated IL-8 attracts neutrophils and other inflammatory cells to the vascular wall, promoting vascular injury, while increased IL-6

contributes to vascular remodeling through cell proliferation. Increased VEGF-A suggests enhanced vascular permeability, potentially affecting vessel integrity, whereas its reduction in perineurial cells highlights differential cellular responses. These cytokine alterations are consistent with clinical observations, strengthening the hypothesis that VZV induces vascular inflammation even in the absence of extensive immune cell infiltration.

Investigations have also demonstrated how plasma exosomes—small extracellular vesicles released by infected cells during HZ—contribute to increased thrombotic risk and stroke. Studies analyzing patients during and after HZ episodes revealed that exosomes carry a pro-thrombotic molecular profile, including proteins associated with platelet activation and coagulation. These exosomes activate platelets in vitro, increase platelet–leukocyte aggregation (a classic marker of hypercoagulability), and stimulate cerebral vascular cells (endothelial and smooth muscle cells) to produce IL-6 and IL-8.

A critical observation from multiple studies is that exosomes collected 2 to 6 months after an HZ episode still retain these hypercoagulable properties, indicating a persistent pro-inflammatory and pro-thrombotic environment driven by the virus.

Inflammation triggered by VZV reactivation increases inflammatory cytokine activity, which inhibits endothelial nitric oxide synthase (eNOS) and enhances inducible nitric oxide synthase (iNOS), leading to excessive nitric oxide production and formation of peroxynitrite ($ONOO^-$), a highly toxic radical. This reduction in functional NO impairs endothelium-dependent vasodilation, including in cerebral arteries, creating a state of impaired vasoreactivity closely associated with ischemic stroke risk, impaired cerebral autoregulation, and hemodynamic instability.

Systemic inflammatory responses activate NADPH oxidase, microglial cells, mitochondrial reactivity, and increase circulating neutrophils and monocytes, resulting in elevated reactive oxygen species (ROS). These ROS oxidize NO, damage the endothelium, promote expression of adhesion molecules (VCAM-1, ICAM-1), and facilitate leukocyte migration, culminating in significant systemic and cerebral endothelial dysfunction.

Persistent inflammation also shifts the endothelium toward a procoagulant state, with increased tissue factor, fibrinogen, P-selectin, and platelet aggregation, along with reduced natural anticoagulants such as thrombomodulin. This mechanism is directly associated with increased risk of ischemic stroke, microthrombosis, and post-inflammatory vascular events following viral infections.

Epidemiological evidence consistently demonstrates that HZ triggers a period of acute cardiovascular risk, particularly in the first weeks following viral reactivation. Stroke risk more than doubles within the first two weeks after HZ, and myocardial infarction risk also increases significantly during this period, supporting the presence of an acute systemic inflammatory trigger.

Herpes zoster ophthalmicus confers an even higher risk. Kim et al. (2020) demonstrated a 1.6-fold increase in stroke risk and a 1.3-fold increase in myocardial infarction risk within the first four weeks, particularly among younger patients and even in the absence of traditional risk factors.

Clinical and epidemiological studies report an early peak in ischemic events (days to weeks) and a modest but persistent increase over longer periods in certain populations. Proposed mechanisms include systemic inflammation from VZV reactivation, endothelial dysfunction, direct viral vasculopathy, and a pro-thrombotic state.

A 2023 observational study analyzed 2,165,505 patients aged ≥18 years receiving care through the Veterans Affairs system, including 71,911 individuals with a history of HZ. The odds ratio for stroke within 30 days after HZ was 1.93 (95% CI: 1.57–2.40; $p < 0.0001$). Vaccination with at least one dose was associated with reduced risk (RZV: OR 0.57 [0.46–0.72]; ZVL: OR 0.77 [0.65–0.91]).

These findings reinforce that HZ is not merely a dermatological condition but a clinically relevant marker of transient vascular risk, justifying closer clinical surveillance and preventive discussions, particularly in high-risk populations.

Horev et al. (2023) conducted a large retrospective cohort study with up to 15 years of follow-up assessing major adverse cardiac and cerebrovascular events (MACCE). The study reported a 19% increased risk in the first year after HZ, with sustained elevation for approximately 4.4 years, adjusted for cardiovascular risk factors. Antiviral therapy did not modify long-term risk in this cohort, reinforcing HZ as a marker of prolonged systemic vascular risk.

Methodologically, the cohort controlled for confounders and analyzed outcomes across temporal windows, showing the greatest relative risk within the first three months, with sustained elevation up to 12 months. These findings suggest that vascular effects of VZV reactivation extend beyond the acute phase.

From a pathophysiological perspective, VZV infects endothelial and vascular neuronal cells, promoting local inflammation, endothelial dysfunction, and extracellular matrix remodeling—processes favoring thrombosis, plaque instability, and chronic vasculopathy.

Clinically, these findings support closer surveillance of patients following HZ, especially those with cardiovascular risk factors or immunosuppression, and reinforce preventive strategies including vaccination.

Vaccination against HZ prevents viral reactivation in sensory nerve fibers and ganglia, thereby interrupting inflammatory cascades before endothelial infiltration and immune activation occur. By preventing reactivation, vaccination indirectly protects cardiovascular health by reducing pro-thrombotic mediators, endothelial activation, and cumulative vascular damage.

Populations that benefit most include older adults, immunocompromised individuals, and patients with comorbidities such as diabetes, hypertension, chronic kidney disease, COPD, and dyslipidemia. In these groups, vaccination reduces inflammatory burden and indirectly lowers cardiovascular risk.

Following an HZ episode, cardiovascular risk increases transiently, particularly in the weeks to months thereafter. Patients should therefore receive cardiovascular evaluation and monitoring, including blood pressure, glucose, lipid profile, ECG, and inflammatory biomarkers when indicated. Education on warning signs of myocardial infarction and stroke is essential.

Despite growing evidence, standardized clinical protocols defining follow-up intensity, risk windows, and preventive strategies are lacking. Prospective multicenter studies are needed to define optimal management and prevention strategies.

4. CONCLUSION

The results of this study indicate that herpes zoster should be understood as a multisystem condition whose effects extend beyond traditional dermatoneurological involvement. Reactivation of the varicella-zoster virus is associated with inflammatory and immunological mechanisms that promote endothelial dysfunction and vascular instability, contributing to an increased risk of major cardiovascular events following the acute episode. Thus, the study objective was achieved by demonstrating that herpes zoster is associated with additional cardiovascular risk and clinically relevant implications.

The primary contribution of this work lies in reinforcing the recognition of herpes zoster as a clinical marker of systemic risk, particularly in vulnerable populations such as older adults, immunocompromised individuals, and patients with cardiovascular comorbidities. From a practical

standpoint, the findings support the importance of preventive strategies—especially vaccination—and structured clinical follow-up that extends beyond treatment of the acute infection. An interdisciplinary approach facilitates early identification of complications, appropriate management of neuropathic pain, and continuous assessment of residual cardiovascular risk, contributing to improved clinical outcomes.

Despite consistent evidence, this study is subject to limitations inherent to the analyzed designs, including methodological heterogeneity and lack of standardized post-herpes zoster follow-up. Future research should prioritize prospective studies and long-term clinical trials to more precisely define the duration of cardiovascular risk and evaluate the effectiveness of targeted preventive strategies. Investigations focused on individualized risk stratification may further support the development of evidence-based clinical protocols.

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