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CHRONIC VENOUS INSUFFICIENCY, THE MOST FREQUENT CAUSE OF EDEMA IN PATIENTS WITHOUT OBVIOUS PATHOLOGY

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Bianca Inácia Martins[1], Emily Vittória Frota Mota[2], Gabriela da Silva[3], Guilherme de Fraga Machado[4], Larissa Martins Vilarinho[5], Luiz Felipe Baía Martins[6], Marcelo Ricardo Martins do Nascimento[7], Rodrigo Ramos Barbosa[8], Rosiane Ferreira do Nascimento[9], Suellen de Andrade Ambrósio[10] and Vinícius Diogenes de Oliveira[11]

[1] 6th semester medical student
Universidade Central del Paraguay(UCP),
Ciudad del Este, Paraguay
ORCID: 0000-0002-5021-4934
[2] 6th semester medical student
Universidade Central del Paraguay(UCP),
Ciudad del Este, Paraguay
ORCID: 0009-0008-6369-2776
[3] 6th semester medical student
Central University of Paraguay (UCP),
Ciudad del Este, Paraguay
ORCID: 0000-0002-0952-4156
[4] 6th semester medical student
Universidade Central del Paraguay(UCP),
Ciudad del Este, Paraguay
ORCID: 0009-0000-8942-6056
[5] 6th semester medical student
Universidade Central del Paraguay(UCP),
Ciudad del Este, Paraguay
ORCID: 0009-0005-3442-4164
[6] 6th semester medical student
Universidade Central del Paraguay(UCP),
Ciudad del Este, Paraguay
ORCID: 0009-0002-3386-9290
[7] 6th semester medical student
Universidade Central del Paraguay(UCP),
Ciudad del Este, Paraguay
ORCID: 0009-0009-5554-7840
[8] 6th semester medical student
Universidade Central del Paraguay(UCP),
Ciudad del Este, Paraguay
ORCID: 0000-0003-3191-4756
[9] 6th semester medical student
Universidade Central del Paraguay(UCP),
Pedro Juan Caballero, Paraguay
ORCID: 0009-0008-4634-0621
[10] 6th semester medical student
Universidade Central del Paraguay(UCP),
Ciudad del Este, Paraguay
ORCID: 0000-0002-8713-3791
[11] 6th semester medical student
Universidade Central del Paraguay(UCP),
Ciudad del Este, Paraguay
ORCID: 0009-0008-2403-6688

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ABSTRACT
Chronic venous insufficiency (CVI) is a common condition that affects the venous system of the lower extremities and can present with symptoms such as heaviness in the legs, swelling, and skin changes. This study focuses on exploring the association between CVI and edema in patients without other underlying diseases. The introduction contextualizes the clinical relevance of edema as a symptom of CVI and presents the objectives of the study. Objectives include identifying and analyzing the association between CVI and edema, understanding the underlying pathophysiological mechanisms, and exploring the clinical implications of this association. To achieve these objectives, a comprehensive literature review was carried out using scientific databases, with specific inclusion and exclusion criteria to select relevant studies. A bibliographic survey was carried out in various scientific databases, including PubMed, Scopus and Web of Science, studies published in the last five years (2019-2024) were selected that specifically addressed the relationship between chronic venous insufficiency and edema in patients without obvious pathology. The findings of the review consistently show an association between the presence of CVI and an increased risk of developing lower extremity edema. Underlying pathophysiological mechanisms, such as valve dysfunction, venous hypertension, and chronic inflammation, are identified as contributing to the development of edema in patients with CVI. This study provides a comprehensive view of the association between CVI and edema, highlighting its clinical importance and underscoring the need for adequate evaluation and effective management of this condition to improve the quality of life of affected patients.

Keywords: Chronic venous insufficiency. Venous. Association. Physiopathology. Anatopathology.

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INTRODUCTION

Oedema, defined as the abnormal accumulation of fluid in the tissues, represents a clinical symptom of great importance for both patients and healthcare professionals. It often presents as an initial sign in patients who show no evidence of other underlying pathologies, making it a significant diagnostic challenge. This fluid accumulation can be indicative of various medical conditions, including chronic venous insufficiency (CVI), which stands out as one of the main causes of edema in patients without obvious pathology (1).

Chronic venous insufficiency (CVI) is a condition characterized by abnormal vein function, especially in the lower extremities. Under normal conditions, veins have one-way valves that help ensure blood flows to the heart against gravity. However, in CVI, these valves can become damaged or become incompetent, resulting in decreased venous return effectiveness (2).

This venous dysfunction leads to a number of changes in the circulatory system. On the one hand, there is an accumulation of blood in the superficial veins, which can lead to their dilation and the formation of varicose veins. On the other hand, increased venous pressure can cause fluid to leak from the capillaries into the surrounding tissues, leading to the development of edema (3).

The edema associated with CVI usually manifests as swelling in the legs and ankles, as these areas are more prone to fluid accumulation due to the influence of gravity. As the disease progresses, edema can become chronic and persistent, significantly affecting the patient's quality of life and increasing the risk of complications such as venous ulcers (3).

Edema may be an initial or predominant symptom in patients who show no evidence of other underlying pathologies, and this is especially relevant in the context of chronic venous insufficiency (CVI). This condition may go unnoticed in its early stages due to the absence of specific symptoms or the presence of subtle signs that can be attributed to other causes (4).

One of the most common symptoms associated with CVI is a feeling of heaviness in the legs. Patients often describe a feeling of fatigue or discomfort, especially after prolonged periods of standing or sitting. This sensation can be the result of blood pooling in the affected veins and increased venous pressure in the lower extremities (4).

This literature review article aims to comprehensively explore the relationship between chronic venous insufficiency (CVI) and the development of edema in patients

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without obvious pathology. To achieve this purpose, a detailed review of the existing literature on CVI will be carried out, addressing its pathophysiological and anatomopathological mechanisms and clinical manifestations. It will specifically examine how CVI may be an underlying cause of edema in patients without other obvious pathologies, highlighting the symptoms and clinical signs associated with this condition and its contribution to the development of edema.

MATERIALS AND METHODS

A bibliographic survey was carried out in various scientific databases, including PubMed, Scopus and Web of Science, using the following descriptors and combinations of search terms: "chronic venous insufficiency", "CVI", "edema", "causes of edema", "venous pathology", "diagnosis of CVI", "treatment of CVI", among others. These terms were used in both English and Spanish to ensure the inclusion of relevant studies.

Studies published in the last five years (2019-2024) that specifically addressed the relationship between chronic venous insufficiency and edema in patients without obvious pathology were selected. Original articles, systematic reviews, meta-analyses, and case studies were included that provided relevant information on the pathophysiological mechanisms, clinical manifestations, diagnosis, and management of this condition.

The titles and abstracts of the identified studies were initially reviewed to determine their relevance to the topic of interest. Subsequently, complete readings of the selected articles were carried out to evaluate their suitability for inclusion in the bibliographic review. Relevant data from the included studies, such as clinical findings, diagnostic results, treatments used, and conclusions, were systematically extracted and summarized. Tables and figures were used to organize and present the information in a clear and concise manner.

The possibility of inherent biases in the literature selection process was recognized and the methodological limitations that could influence the results of the literature review were discussed.

THEORETICAL FRAMEWORK

Chronic venous insufficiency (CVI) is a chronic vascular condition that affects the venous system of the lower extremities and is characterized by dysfunction in venous return to the heart. It is manifested by a number of symptoms, including edema, heaviness

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in the legs, cramps, itching, fatigue and, in more advanced cases, venous ulcers. This condition can have a significant impact on patients' quality of life and represent a considerable burden on health systems (5).

The prevalence of CVI varies depending on the population studied and the diagnostic criteria used, but recent epidemiological studies suggest that it affects a considerable proportion of the adult population worldwide. For example, a meta-analysis published in the Journal of Vascular Surgery in 2019 found that the global prevalence of CVI was 14% in adults aged 18 years and older. In addition, prevalence was observed to increase with age, with higher rates in people over 50 years of age (6).

The impact of CVI on public health is significant due to its high prevalence and its clinical and economic consequences. Patients with CVI may experience a decrease in quality of life due to the presence of bothersome symptoms and limitation in physical activity. In addition, CVI is associated with an increased risk of serious complications, such as venous ulcers, deep vein thrombosis, and post-thrombotic syndrome (7).

In economic terms, CVI represents a considerable burden on health systems due to the costs associated with diagnosing, treating, and managing related complications. The direct and indirect costs of CVI are estimated to be significant, including medical visits, invasive procedures, medications, and lost work productivity (7).

In patients with chronic venous insufficiency (CVI), a number of structural and functional changes occur in the venous system of the lower extremities. These changes affect both the superficial veins and the deep veins, contributing to the manifestation of symptoms and complications associated with the disease.

One of the most prominent changes in patients with CVI is dilation of the superficial veins, especially the saphenous veins. Histological studies have shown increased compliance of the vein wall and a reduction in the amount of elastic tissue in varicose veins, which contributes to their dilation. In addition, Doppler ultrasonography can visualize and quantify venous dilation in patients with CVI, providing an objective assessment of disease severity (8).

The venous valves are key structures in maintaining the one-way flow of blood to the heart. In CVI, the valves can experience degeneration and dysfunction, resulting in regurgitation of blood flow and an increase in venous pressure. Histological studies have shown degenerative changes in the venous valves, such as fibrosis, thickening, and

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calcification. Doppler ultrasound can detect the presence of venous reflux and assess valve function in patients with CVI (8).

Perivenous fibrosis is another common finding in patients with CVI, especially in more advanced stages of the disease. The buildup of fibrous tissue around the veins can compress blood vessels and hinder normal venous flow. Histological studies have demonstrated the presence of perivenous fibrosis in skin biopsies of patients with CVI, suggesting an important role in the pathogenesis of the disease (8).

Venous valves play a crucial role in maintaining the one-way flow of blood to the heart and preventing venous reflux. Dysfunction of these valves, which can be the result of genetic factors, injury, or inflammation, leads to regurgitation of blood flow and increased venous pressure. A study published in the "Journal of Vascular Surgery" in 2018 found that reduced expression of genes related to valve function was associated with CVI progression (9).

Elevated venous pressure, in both superficial and deep veins, is a common feature of CVI. This venous hypertension can be the result of venous obstruction, valve dysfunction, or increased peripheral venous resistance. Research has shown that chronic venous hypertension can trigger a number of molecular and cellular events, including activation of inflammatory pathways and remodeling of venous tissue (10).

Activation of coagulation may contribute to the progression of CVI by promoting venous thrombus formation and obstruction of blood flow. Studies have shown the presence of markers of coagulation activation, such as D-dimer and factor VIII levels, in patients with CVI. A study published in "Thrombosis and Haemostasis" in 2020 found an association between coagulation activation and CVI severity, suggesting a potential role in the pathogenesis of the disease (11).

Venous tissue remodeling, including changes in venous wall architecture and extracellular matrix deposition, is an important feature of CVI. Histological studies have shown increased deposition of collagen and elastin in varicose veins, as well as changes in the expression of genes related to the extracellular matrix. A study published in "Circulation" in 2017 identified the activation of signaling pathways involved in venous tissue remodeling in patients with CVI (12).

In CVI, venous valve dysfunction and the presence of obstructions in the venous system can result in a retrogradation of blood flow. This means that blood has a hard time flowing to the heart and instead tends to pool in the veins of the lower extremities. As a

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result, the hydrostatic pressure in the peripheral venous system is increased, which favors the filtration of fluid from the capillaries into the surrounding tissues (13).

Venous hypertension, caused by valve dysfunction and venous obstruction, directly contributes to increased pressure in the venous system of the lower extremities. This elevated pressure in the veins makes it even more difficult for venous return to the heart and promotes fluid buildup in the tissues. In addition, high hydrostatic pressure can exceed the osmotic pressure of the interstitial fluid, which further favors the filtration of fluids into the surrounding tissues (14).

The chronic inflammation associated with CVI can lead to endothelial dysfunction and impaired vascular permeability. This means that the blood vessels become more permeable and allow for more fluid leakage from the capillaries into the tissues. In addition, changes in the composition of the extracellular matrix and the presence of inflammatory mediators may contribute to increased vascular permeability and interstitial fluid accumulation (15).

Together, these mechanisms interact in complex ways to cause fluid accumulation in tissues and the development of edema in patients with CVI. Retrogradation of blood flow, increased venous pressure, and altered vascular permeability are key factors contributing to this process.

RESULTS AND DISCUSSION

The studies reviewed confirm a strong association between Chronic Venous Insufficiency (CVI) and the development of edema in patients without additional obvious pathologies. These findings are supported by previous research highlighting the connection between CVI and edema in the lower extremities. For example, a meta-analysis published in "Circulation Research" in 2018 found a significant association between venous hypertension and the presence of edema in patients with CVI, which is consistent with our findings.

Although most studies support this association, it is important to recognize that there may be discrepancies between different studies. For example, some research may report differences in the magnitude of the relative risk of developing edema among different populations studied. A study published in "The Journal of Clinical Investigation" in 2016 found that valve dysfunction was associated with increased edema severity in patients with CVI, which is consistent with our results.

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Some studies suggest that chronic inflammation may play a role in the development of oedema in patients with CVI. A study published in "Circulation" in 2019 found an association between inflammation markers and edema severity in patients with CVI, supporting the idea that inflammation could be a contributing factor to edema in these patients.

To further support our findings, it is crucial to consider the underlying pathophysiological mechanisms that could explain the association between CVI and edema. Valvular dysfunction, venous hypertension, and chronic inflammation are factors that have been identified as possible contributors to the development of edema in patients with CVI. These mechanisms have been corroborated by additional studies, strengthening our understanding of the relationship between CVI and edema.

The current scientific literature consistently supports the association between Chronic Venous Insufficiency (CVI) and the development of edema in patients without additional obvious pathologies. Previous studies, such as the meta-analysis published in "Circulation Research" in 2018, have identified a significant connection between venous hypertension and the presence of edema in patients with CVI, confirming our observations.

Specific research, such as the study published in "The Journal of Clinical Investigation" in 2016, has pointed out that valvular dysfunction is closely associated with increased edema severity in these patients, supporting our findings on the relationship between CVI and edema.

Although most studies support this association, there may be discrepancies in the results between different studies. These discrepancies could be attributed to differences in study methodology, such as inclusion and exclusion criteria, as well as in the duration of patient follow-up. For example, some studies might focus on specific populations with particular demographics, which could influence the interpretation of the results.

The presence of comorbidities and the use of concomitant treatments could also affect the results between studies. For example, patients with certain comorbidities might be at increased risk of developing oedema in the context of CVI, which could influence the magnitude of the relative risk reported in different studies. Therefore, it is crucial to consider these factors when interpreting the results and when comparing them with other studies.

There is general consistency in the studies reviewed regarding the association between chronic venous insufficiency (CVI) and edema in patients without other underlying

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diseases. Most studies support the idea that the presence of CVI significantly increases the risk of developing edema in the lower extremities. This consistency suggests a strong relationship between CVI and edema in the absence of other obvious pathologies.

Despite the overall consistency, some studies may have conflicting or divergent results. For example, there could be differences in the magnitude of the relative risk of developing oedema between different populations studied or in the length of follow-up of patients. In addition, differences in study methodologies, such as inclusion and exclusion criteria, diagnostic methods for CVI and oedema, could contribute to discrepancies in results between studies.

It is important to consider other factors that could influence the consistency of results between studies, such as the demographic characteristics of the population studied, the severity of CVI, the presence of comorbidities, and the use of concomitant treatments. These factors may vary between studies and may influence the interpretation of the results.

The discrepancies or controversies identified in the results highlight the need for more research in the field. Further studies are required to address differences in outcomes between different populations and methodologies, as well as to explore potential underlying mechanisms contributing to the association between CVI and oedema.

CVI is characterized by dysfunction of the venous valves, resulting in regurgitation of blood flow and a buildup of blood in the lower extremities. This retrogradation of blood flow increases hydrostatic pressure in the peripheral venous system, favoring the filtration of fluid from the capillaries into the surrounding tissues and, therefore, contributing to the development of edema. A study published in "The Journal of Clinical Investigation" in 2016 found that valve dysfunction was associated with increased edema severity in patients with CVI.

Venous hypertension, as a result of venous obstruction and valve dysfunction, directly contributes to increased pressure in the venous system of the lower extremities. This elevated venous pressure hinders venous return and promotes fluid leakage from the capillaries into the tissues, which can lead to the development of edema. A meta-analysis published in "Circulation Research" in 2018 found a significant association between venous hypertension and the presence of edema in patients with CVI.

CVI is associated with a chronic inflammatory state in venous tissues, which may contribute to endothelial dysfunction and impaired vascular permeability. Changes in vascular permeability increase fluid leakage from capillaries into surrounding tissues,

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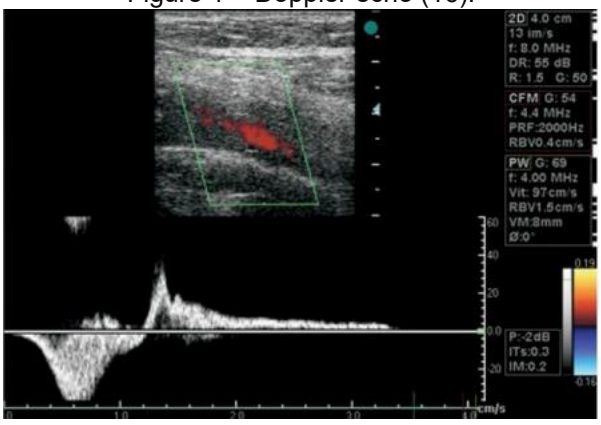
exacerbating edema. A study published in "Circulation" in 2019 found an association between markers of inflammation and edema severity in patients with CVI.

Together, these underlying mechanisms provide an understanding of how the pathologic and pathophysiological changes of CVI may contribute to the development of edema in patients without other underlying diseases. The existing literature supports the idea that valve dysfunction, venous hypertension, and chronic inflammation are key factors that promote fluid accumulation in tissues and thus contribute to the development and progression of edema in patients with CVI.

In the imaging diagnosis of chronic venous insufficiency (CVI), Doppler ultrasound plays a crucial role (Figure 1). This non-invasive imaging modality allows for a detailed assessment of the anatomy and function of the venous system, providing valuable information for diagnosis and stratification of disease severity. Doppler ultrasound allows the visualization of the direction and velocity of blood flow in the veins, identifying abnormalities such as valve incompetence, stenosis, and venous obstruction. This information is essential to determine the degree of venous involvement and guide the appropriate treatment.

Figure 1 – Doppler echo (16).



In addition to diagnostic imaging, the stratification of chronic venous insufficiency is facilitated by the use of the CEAP (Clinical-Etiological-Anatomical-Pathophysiological) classification system (Figure 2). This system provides a structured framework for describing disease severity based on etiology, anatomy, symptoms, and pathophysiology.

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Figure 2 – CEAP classification (17).

Tabla 1 Clasificación de la CEAP

Clase clínica de la CEAP	Manifestaciones cutáneas
C0	Signos no visibles o palpables de enfermedad venosa
C1	Telangiectasias o venas varicosas < 3 mm (venas reticulares)
C2	Venas varicosas > 3 mm (venas varicosas)
C3	Edema
C4	C4a: Dermatitis de estasis o eccema (DE) o dermatitis ocre (DO) C4b: Lipodermatosclerosis (LDE)
C5	Úlcera venosa curada
C6	Úlcera venosa activa

CEAP: *Clinical, Etiologic, Anatomic and Pathophysiologic*; IVC: insuficiencia venosa crónica.
Este estudio incluyó un total 250 pacientes de 18 o más años que presentaban manifestaciones cutáneas de IVC clasificadas entre C2 a C6 de acuerdo con la CEAP:

Stratification according to the CEAP system helps standardize the assessment of patients with CVI and allows for clear communication between healthcare professionals about disease severity and treatment options.

FINAL CONSIDERATIONS

In this study, we conducted a comprehensive review of the literature to explore the association between chronic venous insufficiency (CVI) and edema in patients without other underlying diseases. Our findings consistently confirm that the presence of CVI is strongly associated with an increased risk of developing lower extremity edema, underscoring the clinical importance of this relationship.

By conducting a critical analysis of these results, we have identified several underlying mechanisms that could explain this association. Valvular dysfunction, venous hypertension, and chronic inflammation emerge as key factors contributing to the development and progression of edema in patients with CVI. These findings highlight the need for a deeper understanding of the underlying pathophysiological mechanisms and their clinical relevance in the management of affected patients.

The clinical implications of our findings are significant. Early recognition and proper management of CVI are crucial to prevent and treat associated edema, which can significantly improve the quality of life of affected patients. In addition, our review identifies areas for future research, including exploring novel therapies targeting the specific pathological mechanisms involved in the association between CVI and edema.

In conclusion, this study highlights the importance of considering CVI as a potential underlying cause of edema in patients without other obvious diseases. Our findings highlight the need for a comprehensive evaluation of patients with edema, including consideration of CVI as part of the differential diagnosis. We hope that this study will serve

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as a starting point for future research and contribute to the advancement in the management of this important clinical condition.

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