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Subcutaneous Ossification as a Rare Complication of Chronic Venous Insufficiency

Potkožna osifikacija kao rijetka komplikacija kronične venske insuficijencije

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Abstract. Chronic venous insufficiency is a condition caused by dysfunction of the venous valves, which hinders venous blood return and increases hydrostatic pressure. This can lead to the appearance of telangiectasia, varicose veins, hyperpigmentation, eczema, lipodermatosclerosis, and in more severe cases, venous ulcers. Long-term chronic venous insufficiency can lead to a rare complication – subcutaneous ossification, which was first described by Lippman in 1957. Dystrophic calcification, which occurs in chronic venous insufficiency, causes deposition of calcium in the subcutaneous tissue, which can interfere with ulcer healing and contribute to the development of heterotopic ossification. Heterotopic ossification is an abnormal formation of bones in the extraskeletal tissue, which most often occurs after trauma, orthopaedic procedures or in neurological disorders. Although the exact mechanism of heterotopic ossification development in chronic venous insufficiency is not fully elucidated, research indicates that inflammatory processes and increased activity of alkaline phosphatase can lead to calcium accumulation, leading to the formation of bone structures. In patients with venous insufficiency, calcifications most often appear as phleboliths, with a characteristic appearance on X-rays. Histologically, heterotopic ossification shows a zonal bone structure with a peripheral area of ossification, while in later stages it resembles a normal bone structure. Treatment includes surgical removal as the optimal method, while conservative treatments such as sodium thiosulfate and etidronate can be used to slow the progression of calcifications.

Keywords: leg ulcer; metaplasia; ossification; venous insufficiency

Sažetak. Kronična venska insuficijencija stanje je koje nastaje zbog disfunkcije venskih zalisaka, što otežava venski povrat krvi i povećava hidrostatski tlak. Time može dovesti do pojave telangiektazija, varikoznih vena, hiperpigmentacije, ekcema, lipodermatoskleroze, a u težim slučajevima i do venskih ulkusa. Dugotrajna venska insuficijencija može dovesti do rijetke komplikacije – supkutane osifikacije, koju je prvi put opisao Lippman 1957. godine. Distrofična kalcifikacija, koja se javlja u kroničnoj venskoj insuficijenciji, predstavlja taloženje kalcija u supkutano tkivo, što može ometati zarastanje ulkusa i pridonijeti razvoju heterotopične osifikacije. Heterotopična osifikacija je abnormalno formiranje kosti u ekstraskeletalnom tkivu koje se najčešće javlja nakon trauma, ortopedskih zahvata ili u neurološkim poremećajima. Iako točan mehanizam razvoja heterotopne osifikacije u okviru kronične venske insuficijencije nije potpuno razjašnjen, istraživanja upućuju na to da upalni procesi i povećana aktivnost alkalne fosfataze mogu dovesti do nakupljanja kalcija, što dovodi do stvaranja koštanih struktura. Kod pacijenata s venskom insuficijencijom kalcifikacije se najčešće javljaju kao fleboliti, s karakterističnim izgledom na rendgenskim snimcima. Histološki, heterotopna osifikacija pokazuje zonalnu koštanu strukturu s perifernim područjem osifikacije, dok u kasnijim fazama postaje slična normalnoj koštanoj strukturi. Liječenje uključuje kirurško uklanjanje kao optimalnu metodu, dok se konzervativni tretmani kao što su natrijev tiosulfat i etidronat mogu koristiti za usporavanje razvoja kalcifikacija.

Ključne riječi: metaplazija; osifikacija; ulkus noge; venska insuficijencija

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INTRODUCTION

Chronic venous insufficiency (CVI) is a condition that occurs because of dysfunction of the venous valves, which makes a venous return of blood difficult[1]. Due to venous insufficiency, hydrostatic pressure increases, leading to the appearance of telangiectasias, the development of varicose veins, hyperpigmentation, eczema, lipodermatosclerosis, and ultimately to venous ulcers[1–4].

The prevalence of chronic venous insufficiency ranges from 1 to 40% in women, and 1-17% in men[1]. Long-term venous insufficiency can lead to the development of a rare complication, subcutaneous ossification[3]. The first case of subcutaneous ossification as part of chronic venous insufficiency was described by Lippman in 1957 [5]. Then, in 1960, Lippman and Goldin published a study that included 600 patients with chronic venous insufficiency, and subcutaneous ossification occurred in 10% of the subjects[3, 6].

Dystrophic calcification is a condition in which calcium salts are deposited in the subcutaneous tissue[4, 7, 8]. It has its clinical importance as it can potentially stimulate the development of heterotopic ossification (HO)[8]. HO is defined as abnormal bone formation in extraskeletal tissue, accompanied by increased osteoblast activity[3]. This paper aims to present an overview of data from the available literature on subcutaneous ossification and to indicate the pathogenetic mechanisms by which the development of ulcers in chronic venous insufficiency is promoted.

EPIDEMIOLOGY

If it occurs in young adulthood, HO mainly presents in areas that are often exposed to trauma (elbow, thigh, pelvis, and shoulders). It affects men 1.5 times more frequently than women. It also emerges after orthopaedic procedures such as hip arthroplasty, as well as bone fractures and dislocations. It is also often seen in neurological disorders, traumatic head and spine injuries and extensive burns. The incidence of HO in traumatic amputations is as high as 90%[8]. Alternatively put, HO occurs where stromal cells are abundant. Exceptions are the visceral organs and the diaphragm, where osteogenic lesions rarely appear[8].

Lippman first reported a link between subcutaneous HO and CVI in 1957, observing it in 23 patients, with an additional 37 cases later suggesting an overall occurrence rate of about 10% in CVI[6, 9]. Since then, a few isolated cases have been documented, and the limited existing reviews mainly focus on CVI and subcutaneous dystrophic calcification identified through imaging studies. One review reported calcification in 17.5% of 40 CVI cases, while another found it in 65% of 20 patients with long-standing, severe CVI. Among those who underwent biopsy, SCHO was present in 20% of cases[9].

Calcium deposits act as a foreign body and cause permanent inflammation hindering the growth of epithelial cells and inhibiting the healing of an ulcer wound.

CLINICAL FEATURES AND PATHOGENESIS

Dystrophic calcification is a condition in which calcium salts are deposited in the subcutaneous tissue [4, 8].

Tissue trauma, followed by degeneration of collagen and elastic fibres, fatty tissue necrosis, infection, and neoplasm are all mentioned as the main determining factor[4]. Chronic venous insufficiency (CVI) is also considered a risk entity with underlying inflammation as pathophysiological factor. In addition, studies have shown that deposits of calcium salts in the skin significantly inhibit the healing process of ulcers, which ultimately leads to the development of refractory ulcers[4]. Namely, calcium deposits act as a foreign body and cause permanent inflammation hindering the growth of epithelial cells and inhibiting the healing of an ulcer wound (Figure 1)[4]. Regarding the long-term follow-up of patients with severe resistant ulcers, it is recommended to carry out periodic X-ray examinations to identify latent calcifications and prevent resistant ulcers[4].

The prevalence of calcification increases with the duration of the disease itself. According to the radiography finding, there is a distinguishment, between reticular, trabecular and punctiform

calcifications (Figure 2). The latter two are most often found in people with chronic venous insufficiency[4]. The pathogenesis of dystrophic calcification has not been fully elucidated, but it is believed to be caused by inflammation triggered by the venous pathway, due to which phosphates bind to denatured proteins[4, 7]. Another pathogenetic mechanism described in the literature refers to the increased activity of alkaline phosphatase, which causes the hydrolysis of extracellular pyrophosphates, which normally inhibit calcium deposition[7]. In cases of trauma, pro-inflammatory cytokines boost the activity of stromal cells and guide them to the osteogenic formation during the inflammatory response that follows trauma[8].

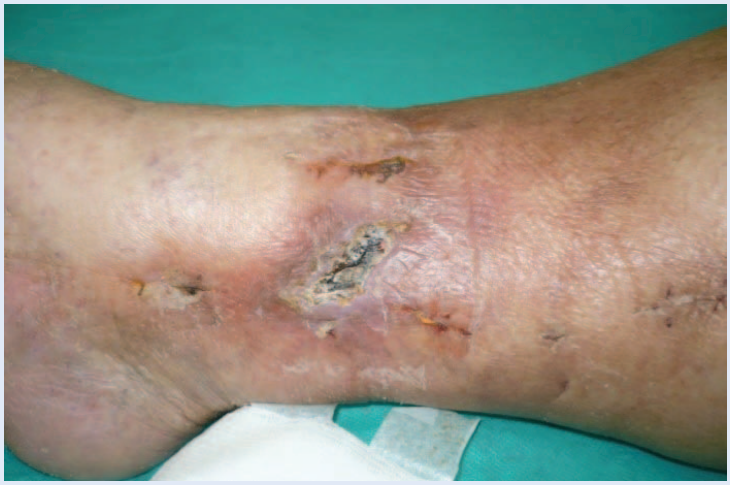

Figure 1. Ulcer after surgical treatment (phlebectomy) of CVI and partial subcutaneous calcifications removal (at the site of the wound crust)

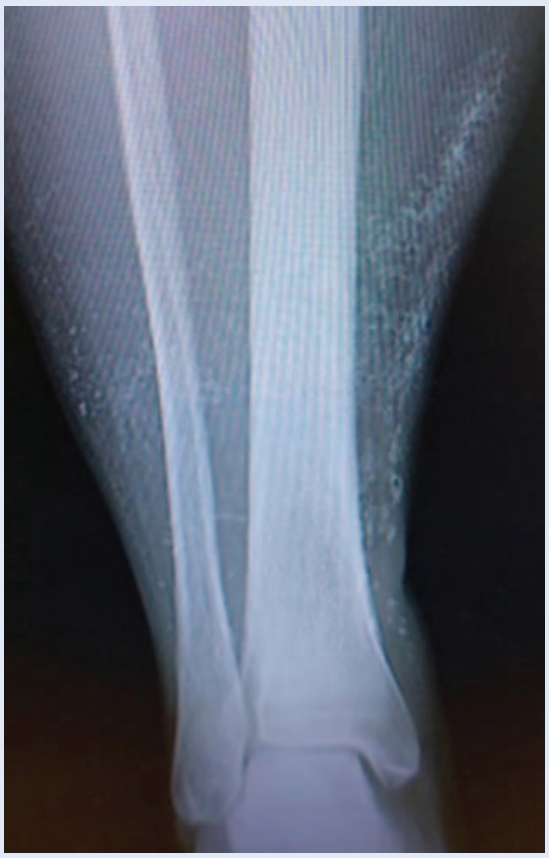

Figure 2. Radiological finding of punctiform and reticular subcutaneous calcification

In addition to CVI, dystrophic calcification can also occur in other systemic diseases, such as systemic sclerosis, dermatomyositis and, systemic lupus erythematosus[7, 3, 8]. The morphological pattern of dystrophic calcification differs in various clinical entities. For example, in systemic sclerosis and SLE occurs in smaller clusters, while in late-stage dermatomyositis, it is presented in the form of widespread deposits[3].

Dystrophic calcification has clinical importance insofar as it can potentially enhance the development of HO[8].

Heterotopic ossification (HO), also known as Heinz-Lippmann disease (HL), is defined as abnormal bone formation in extraskeletal tissue, accompanied by increased osteoblast activity[3]. There is a distinction between genetic and non-genetic forms of HO[8]. It mainly occurs in the area of surgical incisions, musculoskeletal trauma, skin neoplasms, as well as in regions of skin affected by changes due to chronic venous insufficiency, etc[3, 8]. The pathogenesis is not completely known, however, since HO most often occurs in post-menopausal women, it is assumed that hormonal imbalance plays a role in the alteration of subcutaneous tissue into viable bone[3].

In heterotopic calcification, serum calcium and phosphate values are within the reference intervals, while they are elevated in metastatic calcification and calciphylaxis. Metastatic calcification occurs primarily as a result of elevated calcium and/or phosphate values in patients with hypervitaminosis D or milk alkali syndrome. As in Heinz-Lippmann disease, metastatic calcification presents as periarticular calcification. Calciphylaxis most often occurs as part of chronic renal failure[3].

The subcutaneous tissue of the extremities consists mainly of fatty tissue with small amounts of connective, vascular and nervous tissue. Given the large proportion of fatty tissue, radiography is usually not of great importance in the diagnosis of the pathological condition of the subcutaneous tissue. However, the presence of abnormal calcifications is one of the exceptions and their presence is easily noticeable with a relatively lucent background of subcutaneous tissue. When they are present, they are often the result of one of the following conditions and diseases: tumoral calcinosis, end-stage chronic kidney disease, systemic sclerosis, or venous insufficiency. A thorough knowledge of the typical appearance of calcifications associated with these entities, as well as the clinical context in which they appear, is essential for diagnostic accuracy.

On radiographs of the extremities, calcifications of chronic venous insufficiency most often appear as phleboliths in the subcutaneous tissue. They have a characteristic ring shape with a radiolucent centre that represents the focus of a calcified thrombus. Also, they are often presented as small, linear calcifications oriented along the longitudinal axis of the limb. In these cases, numerous calcifications are typically present, which are often parallel to each other or give a reticular pattern. Apart from calcification, other signs of chronic venous stasis may be present, such as oedema of soft tissues or even periosteal bone reactions[10].

The radiological appearance of the pathological substrate of HO disease is phasic and dynamic, which reflects the subsequent changes that occur due to ossification. The classic appearance of mature intramuscular HO is a well-developed and sharply circumscribed mass, with a zone of ossification most prominent at the periphery giving the mass a calcified outline, termed “eggshell calcification”.

Early lesions may present as focal opacities without a clear zone of ossification. HO most often occurs in soft tissue, however, with further growth, it can be attached to the surface of the bone, resulting in periosteal HO. Over time, it can cause ankylosis of the joint[8].

The clinical presentation depends on the time stage of HO development. In the early, inflammatory phase, HO is manifested by localized pain, tenderness and swelling. During this time, HO is often characterized by a rapid increase in size, which may raise the clinical suspicion of sarcoma. In the later stages and with the gradual maturation of the bone tissue, the swelling becomes more localized, firmer and, if near the joint, with limitation of movement[8, 9].

Hereditary forms of HO are extremely rare, and two diseases are described in the literature – fibrodysplasia ossificans progressiva (FOP) and progressive osseous heteroplasia (POH)[8].

PATHOHISTOLOGY

Early lesions are usually hypercellular with a small amount of bone matrix. However, over time, the lesion develops into a characteristic bone formation with a zonal structure where ossification zone predominates on the periphery (Figure 3).

Early lesions are characterized by marked hypercellularity and proliferation of stromal cells with a large number of mitoses, scattered multinuclear giant cells and a diffuse infiltrate. As the lesion “ripens”, bone appears with a sheath of osteoblastic cells.

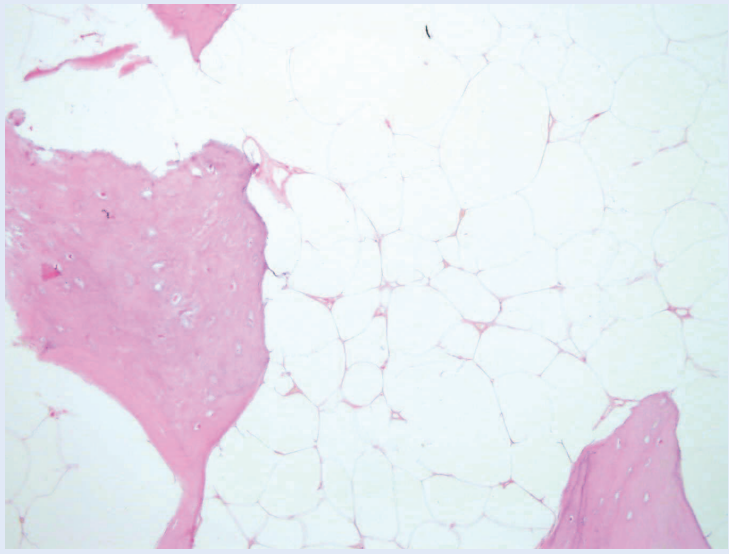

Figure 3. Osseal metaplasia in subcutaneous tissue of the lower leg in the patient with chronic venous insufficiency. Histologically, small fragments of normal bone tissue interspersed with mature adipose tissue. This finding refers to the same patient shown in Figure 1, 2 and 4. HE X200

The HO is well circumscribed, with surrounding fibrosis and a pseudocapsule surrounded by blood vessels. In their mature form, they resemble native bone tissue; it contains trabeculae of lamellar bone with a central fatty marrow and vascular spaces resembling the sinusoids of the bone marrow. On the periphery, it can show compact bone tissue that resembles native cortical bone. Sometimes structures resembling Haversian and Volkmanian canals can be discerned in the sample. The pathological differentiation of HO and extraskeletal sarcoma is extremely important. The histological finding of bone with zones of ossification speaks in favour of HO. The finding of immature bone trabeculae with an osteoblastic rim and progression to more mature bone is not usually found in osteosarcoma. In addition, there will not be cells with nuclear atypia or atypical mitotic figures in HO.

Also, HO associated with the bone surface may present a diagnostic challenge for osteosarcomas arising on the bone surface[8].

Due to favourable microenvironmental conditions (hypoxia, inflammation, mechanical pressure, etc.), which appear as part of CVI, there is activation of signalling pathways in the stem cells of subcutaneous fat, which then differentiate into cell lines with osteogenic potential.

ULTRASOUND

Ossification shows hyperechogenic images with a posterior acoustic shadow artefact in the subcutaneous tissue, while calcifications are less echogenic[9]. It can serve as an orientation examination and early detection of these lesions; however, a final diagnosis is made by biopsy.

PATHOPHYSIOLOGY OF HO

The pathophysiology is still not completely known, however, there are several hypotheses. It is believed that under certain microenvironmental conditions, the differentiation of cells of mesenchymal origin, present in the connective tissue, into cells with osteogenic potential occurs[11].

Chalmers et all point out 3 main prerequisites for the development of HO: osteogenic precursor cells, an indicating factor and a permissive environment[12]. A central role in the pathogenesis could be played by the bone morphogenetic protein that acts on the mesenchymal cells of the connective tissue, with previously satisfied microenvironmental conditions. Bone morphogenetic protein (BMP) is probably secreted from the bone in response to venous stasis, inflammation or connective tissue disease, and in conditions accompanying immobilization. By its function, BMP is a growth factor that exerts its effect on target cells by activating the serine-threonine kinase pathway. More than 20 different types of BMPs have been discovered so far, but the BMP-2/4 subfamily stands out for its effect on osteogenesis. Binding of ligands to BMP-2 receptors triggers gene expression, cell differentiation and proliferation, and the production of osteogenic factors. This leads to vascular proliferation and osteogenesis; however, studies have shown that HO requires the interaction of different types of cells[13]. Some studies have recognized the role of non-osteogenic cells in the pathogenesis of HO. In this regard, cells that express Tie2 receptors that undergo endochondral differentiation in the inflammatory medium and form heterotopic foci in response to BMP stimulation stand out. Fibrocytes are also susceptible to differentiation into osteoblasts and chondrocytes and thus contribute to the pathogenesis of HO.

Partial pressure of oxygen (PO2), pH, micronutrients and mechanical stimulation contribute to the development of HO. HIF-1α (hypoxia-inducible factor 1-alpha) is a key transcriptional regulator in the cellular response to ischemia. Namely, it stimulates gene expression of angiogenic cytokines such as VEGF (Eng. Vascular endothelial growth factor), bFGF (Eng. basic fibroblast growth factor), PDGF (Eng. platelet-derived growth factor) and angiopoietin 2. HIF-1α signalling maintains and promotes the differentiation of hypoxic prechondrogenic cells, which are crucial for the development of HO. Mesenchymal stem cells are stromal cells that possess the ability of self-renewal and multilineage differentiation. They can be isolated from different tissues, such as umbili-

cal cord, endometrial polyps, bone marrow, adipose tissue, etc[14]. Nowadays, there is more talk about stem cells obtained from adipose tissue that show the characteristics of pluripotency, which enables them to differentiate into various cell lines, such as chondrocytes, myocytes, osteoblasts[15]. Considering the review of the available literature and current knowledge about HO, it could be assumed that due to favourable microenvironmental conditions (hypoxia, inflammation, mechanical pressure, etc.), which appear as part of CVI, there is activation of signalling pathways in the stem cells of subcutaneous fat, which then differentiate into cell lines with osteogenic potential. However, this hypothesis should be given more attention in future research.

TREATMENT

Surgical debridement is the optimal method of treating dystrophic calcification in patient with lower leg ulcer (Figure 4). Although, the latest studies debate about very effective conservative methods that include the use of sodium thiosulfate, which acts as a calcium chelator and thus creates soluble compounds, calcium phosphate. Etiodronate disodium can slow the further progression of dystrophic calcification[4, 7].

Early finding HO as part of CVI is of great clinical importance, because it's early management prevents further progression and the development of resistant ulcers. If HO is revealed, debridement as a part of chronic ulcer care, and HO excision is recommended[9].

One case report describes a patient with CVI who developed extensive HO with chronic leg ulceration, and treatment included wound debridement and skin grafting, which allowed limb preservation[16]. However, there are very few reports in the literature of HO in the context of CVI, and most of the available data refer to HO after traumatic or military amputations. For example, in one study of civilian amputee patients, 22.8% had symptomatic HO, while in the military population the percentage was significantly higher, 63%[17]. Although the specific percentage of amputations due to HO in CVI is not clearly documented, there are reports that suggest that HO can be a serious complication in patients with CVI, especially in the presence of chronic ulcers. However, due to limited data, further research is needed to more precisely determine the risk of amputation in this population.

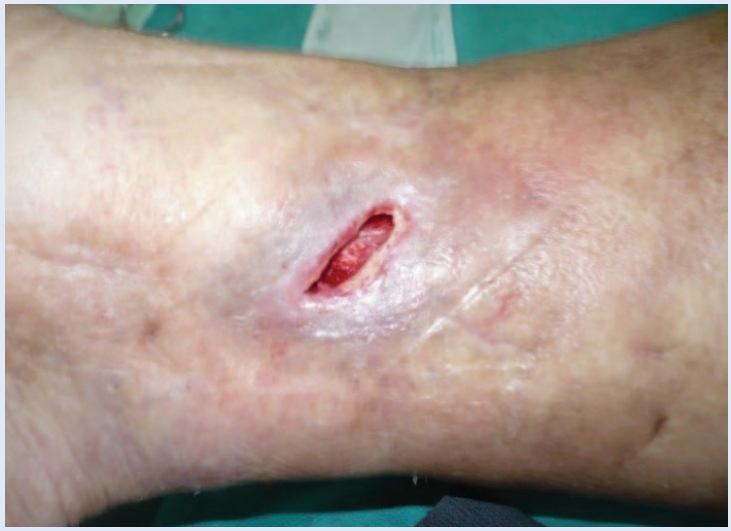

Figure 4. Four weeks after surgical treatment (phlebectomy) *of CVI* and treatment *of the ulcer with dressing*

The management of patients with chronic venous insufficiency (CVI) and peripheral arterial disease (PAD) requiring endovascular or open revascularization represents a significant clinical challenge. In this population, the presence and severity of both vascular disorders significantly influence treatment approach and outcomes. The combination of CVI and PAD may make ulcer healing more difficult and increase the risk of complications. According to a study published in the British Journal of Surgery, patients with moderate arterial damage (ABI 0.5–0.85) who started treatment with modified compression and then underwent revascularization had a healing rate of 75%. On the other hand, patients with severe arterial damage (ABI <0.5) who started with arterial intervention had a lower healing rate of 40% (95% CI 16–66%). These studies suggest that in patients with moderate arterial damage, a venous-first approach is more effective, while in patients with severe arterial damage, it may be necessary to address the arterial problem first[18].

CONCLUSION

Heterotopic ossification (HO) and dystrophic calcification represent significant pathological proc-

esses that often occur in the context of trauma, chronic venous insufficiency (CVI), neurological disorders, orthopaedic procedures, as well as in persons with serious burns or amputations. Although the pathogenesis of HO and dystrophic calcifications is partially explained, there are a number of mechanisms that include inflammatory processes, changes in the microenvironment, and the activation of osteogenic factors such as BMP (bone morphogenetic protein), which leads to abnormal bone formation in soft tissues. The treatment of HO includes surgical debridement of the lesions, while for dystrophic calcifications, conservative methods such as the use of sodium thiosulfate and disodium etidronate are recommended, which can slow down the progression of calcifications. Recognition of HO as part of CVI has clinical significance because surgical debridement or excision of lesions can prevent further progression of the disease and the development of resistant ulcers.

Additional research related to the mechanisms of HO could advance our understanding and treatment of this pathological condition. Especially, in the context of the microenvironmental conditions (hypoxia, inflammation, mechanical pressure, etc.), which appear as part of CVI and the mesenchymal role of stem cells, with activation of signalling pathways in the stem cells of subcutaneous fat, which then differentiate into cell lines with osteogenic potential.

Conflicts of Interest: Authors declare no conflicts of interest.

REFERENCES

1. Patel SK, Surowiec SM. Venous Insufficiency. [Updated 2024 Feb 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430975/
2. Youn YJ, Lee J. Chronic venous insufficiency and varicose veins of the lower extremities. Korean J Intern Med 2019;34:269-283.
3. Toll A, Marsico S, Duitama ICG, López-Aventín D, Claramunt AA, Pujol RM, et al. Heinz-Lippmann disease as an underrecognized cause of chronic venous insufficiency-associated cutaneous ulcers: Clinical and imaging findings. Radiol Case Rep 2020;15:1518–22.
4. Tokoro S, Satoh T, Okubo Y, Igawa K, Yokozeki H. Latent Dystrophic Subcutaneous Calcification in Patients with Chronic Venous Insufficiency. Acta Derm Venereol 2009;89:505–8.
5. Lippmann HI. Subcutaneous Ossification in Chronic Venous Insufficiency: Presentation of 23 Cases: a Preliminary Report: Presentation of 23 Cases: a Preliminary Report. Angiology. 1957;8:378-396.
6. Sarkany I, Kreel L. Subcutaneous Ossification of the Legs in Chronic Venous Stasis. BMJ. 1966;2:20–8.
7. Wolf EK. Topical Sodium Thiosulfate Therapy for Leg Ulcers With Dystrophic Calcification. Arch Dermatol 2008;144:1560.
8. Meyers C, Lisiecki J, Miller S, Levin A, Fayad L, Ding C, et al. Heterotopic Ossification: A Comprehensive Review. JBMR Plus. 2019;3:e 10172.
9. García-Arpa M, Flores-Terry MA, Franco-Muñoz M, Villasanti-Rivas N, González-Ruiz L, Banegas-Illescas ME. Osificación heterotópica de las piernas en un varón. Reumatol Clín 2020;16:300–2.
10. Banks KP, Bui-Mansfield LT, Chew FS, Collinson F. A Compartmental Approach to the Radiographic Evaluation of Soft-Tissue Calcifications. Semin Roentgenol 2005; 40:391–407.
11. Shehab D, Elgazzar AH, Collier BD. Heterotopic ossification. J Nucl Med 2002;43:346-353
12. Chalmers J, Gray DH, Rush J. Observations on the induction of bone in soft tissues. J Bone Joint Surg Br 1975;57-B(1):36–45.
13. Ranganathan K, Loder S, Agarwal S, Wong VW, Wong VC, Forsberg J, et al. Heterotopic Ossification: Basic-Science Principles and Clinical Correlates. JBJS 2015; 97(13): 1101–11.
14. Ding D-C, Shyu W-C, Lin S-Z. Mesenchymal Stem Cells. Cell Transplantation [Internet]. 2011 Feb;20(1):5–14. Available from: https://journals.sagepub.com/doi/full/10.3727/096368910X
15. Miana VV, Prieto González EA. Adipose tissue stem cells in regenerative medicine. ecancermedicalscience [Internet]. 2018 Mar 28;12. Available from: https://ecancer.org/journal/12/full/822-adipose-tissue-stem-cells-in-regenerative-medicine.php
16. Cafasso DE, Bowen DK, Kinkennon SA, Stanbro MD, Kellicut DC. Heterotopic ossificans in chronic venous insufficiency: a new consideration for clinical, aetiology, anatomy and pathophysiology staging. Phleb 2013;28: 361–5.
17. Matsumoto ME, Khan M, Jayabalan P, Ziebarth J, Munin MC. Heterotopic ossification in civilians with lower limb amputations. Arch Phys Med Rehabil 2014;95:1710-3.
18. Alagha M, Alagha A, Lowery A, Walsh SR. "Veins first" versus "artery first" approach for management of mixed arterial venous leg ulcers (MAVLU): Systematic review and meta-analysis. Phleb 2025;40:144-152.