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CONTINUING EDUCATION

Consultant Pharmacist Continuing Education Series

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Peripheral oedema

Peripheral oedema is non-specific symptom common among older persons and is characterised by swelling of lower legs or hands. It results from accumulation of fluid causing swelling. There are a wide range of causes, from sitting or standing too long to many conditions such as heart failure and renal disease. It is most often caused by extravasation of fluid from veins and arteries into the fluid-filled spaces or interstitium that underlies the skin and surrounds internal organs.

Symptoms

Peripheral oedema should be assessed for pitting, tenderness and skin changes. Timing of oedema is important to assess, along with any changes with position, and whether it is unilateral or bilateral. Unilateral oedema suggests deep vein thrombosis (DVT), cellulitis or lymphatic obstruction. Whereas bilateral oedema suggests systemic diseases such as heart failure, liver failure, kidney failure or severe malabsorption syndromes.

Causes

The most common cause of peripheral oedema in people over 50 years of age is venous insufficiency and related to aging. Peripheral oedema can be generalised or localised.

Localised peripheral oedema may be caused by lymphoedema, lipoedema, DVT, dermatitis and cellulitis. Lymphoedema is caused by inadequate lymphatic drainage and is typically non-pitting. Acute DVTs are usually associated with unilateral swelling, pain and sometimes erythema. Localised skin irritations can lead to dermatitis or eczema, with patients experiencing pain, erythema, or pruritus. People with cellulitis will complain of tenderness or pain and erythema, and may also have fever.

Conditions associated with generalised peripheral oedema include:

- Heart failure
- Constrictive pericarditis
- Restrictive cardiomyopathy
- Hepatic cirrhosis
- Nephrotic syndrome
- End-stage renal failure
- Acute renal failure
- Nutritional deficiencies
- Medications

Heart failure is a common cause of generalised peripheral oedema. In heart failure, the inability of the heart to effectively circulate blood throughout the body leads to increased venous pressure that is transmitted to the capillaries. This causes extravasation of electrolytes and fluid into the interstitium, causing oedema. The low output caused by heart failure also leads to the release of neurohormones of the renin-angiotensin-aldosterone system (RAAS) which causes sodium and water retention.

Pericarditis and cardiomyopathy are less common causes of peripheral oedema. People with these conditions experience shortness of breath, and often have signs of hepatic congestion and ascites as well as peripheral oedema.

End-stage liver disease, predominantly caused by ascites, also causes peripheral oedema. Oedema is due to severe low albumin, and salt and water retention.

Nephrotic syndrome, acute renal failure and end-stage renal failure can all give rise to peripheral oedema. Nephrotic syndrome is characterised by peripheral oedema in association with high-level proteinuria, low serum albumin levels and high serum cholesterol levels. Diabetic nephropathy is a common cause of proteinuria in adults.

Severe nutritional deficiency can lead to low serum albumin and protein levels, which causes peripheral oedema. Peripheral oedema is also seen in overweight and obese people.

Lipoedema is caused by accumulation of fatty deposits, most commonly in the lower extremities. It can be bilateral and mistaken for lymphoedema or venous incompetence but is differentiated from them by the absence of pitting and of involvement of the feet.

Medication-related peripheral oedema

Peripheral oedema is a common side effect of medications, including:

- Calcium channel blockers - nifedipine, amlodipine, felodipine, lercanidipine
- Vasodilators - minoxidil
- NSAIDs
- Corticosteroids - prednisone, prednisolone
- Antidepressants - escitalopram, mirtazapine, paroxetine, venlafaxine
- Estrogens and progestogens
- Thiazolidinediones - pioglitazone *(Actos)*
- Antiepileptics - carbamazepine, clobazam, valproate
- Antipsychotics - clozapine, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone
- Gabapentinoids - gabapentin, pregabalin
- Aromatase inhibitors - anastrozole *(Arimidex)*, letrozole *(Femara)*
- Analgesics - fentanyl, hydromorphone, morphine, oxycodone, tramadol

Calcium channel blockers

Calcium channel blockers (CCBs) including nifedipine (*Adalat*), amlodipine (*Norvasc*), felodipine (*Plendil*), lercanidipine (*Zanidip*) can cause peripheral oedema in up to 70% of people prescribed them. The incidence of peripheral oedema is lower with newer lipophilic CCB lercanidipine. Verapamil (*Isoptin, Cordilox*) and diltiazem (*Cardizem*) are also calcium channel blockers but are much less likely to cause peripheral oedema.

Peripheral oedema caused by CCBs is usually diffuse with bilateral swelling of feet, ankles and sometimes lower legs. It may also present with lower extremity redness, warmth and non-blanching petechial rash. The oedema typically worsens throughout the day and improves overnight. It is not due to water or sodium retention, rather selective arteriolar vasodilatation.

Gabapentinoids

Gabapentinoids such as gabapentin (*Neurontin*) and pregabalin (*Lyrica*) cause peripheral oedema in about 2% to 16% of patients. Gabapentinoids are prescribed for treatment of epilepsy and neuropathic pain. They are commonly overused in older people for sciatica and low back pain. Evidence only supports use in people with diabetic neuropathy and post-herpetic neuralgia pain syndromes.

The risk of peripheral oedema with gabapentinoids is age and dose-related. Higher dose such as greater than 1800mg per day of gabapentin and more than 300mg per day of pregabalin have a three-fold increased incidence of peripheral oedema. There is also an increased risk among people living with dementia. In this population, decreased mobility or increased risk of being bedridden may further increase likelihood of lower extremity oedema.

A prescribing cascade where a diuretic is added to treat gabapentinoid-induced peripheral oedema can lead to over-diuresis, falls, urinary incontinence and electrolyte imbalances.

Management

Management of peripheral oedema should be guided by the underlying condition. Loop diuretics can be used with heart failure and liver or kidney disease. Diuretics should not be used to treat peripheral oedema caused by medications.

CCBs may be administered at bedtime to reduce oedema. Dosage reduction or switching to another appropriate antihypertensive should be considered. If clinically indicated, the addition of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) to a CCB reduces oedema by about two-thirds.

Management of gabapentinoid-induced peripheral oedema should include a review of the appropriateness and ongoing need for these medicines. If deprescribing is not appropriate, a lower dose could be trialled.

For patients with heart failure who do not require hospitalisation, loop diuretics such as furosemide are used. Treatment for heart failure with reduced ejection fraction (HFrEF) should be optimised with ACE inhibitors, ARB or preferably an ARNI (sacubitril–valsartan) plus a beta-blocker, mineralocorticoid receptor antagonist (MRA) and an SGLT2 inhibitor (dapagliflozin, empagliflozin). In patients with preserved ejection fraction (HFpEF) an SGLT2 inhibitor (empagliflozin) should be considered to decrease cardiovascular mortality or hospitalisation for heart failure.

References
MedicineToday 2015; 16(6): 26-34.
J Clin Hypertens 2004;6:400–2.
J Clin Hypertens 2003;5:291–5.
Br J Clin Pharmacol 2021;87:3043–3055.
Am J Med 2011;124(2):128-135.
J Am Geriatr Soc 2021; 69(10): 2842-2850.
Br J Clin Pharmacol 2022.
Med J Aust 2022.