MONASH University

Drug-induced peripheral oedema

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Drug-induced peripheral oedema is not often recognized and often misdiagnosed, this leads to the prescribing of diuretics and other medication .
Four main causes of oedemas include:

Precapillary arteriolar vasodilation (vasodilatory oedema)
Sodium/water retention (renal oedema)
Lymphatic insufficiency (lymphedema)
Combined Venous and Lymphatic oedema (Phlebolymphoedema
Increased capillary permeability (permeability oedema).

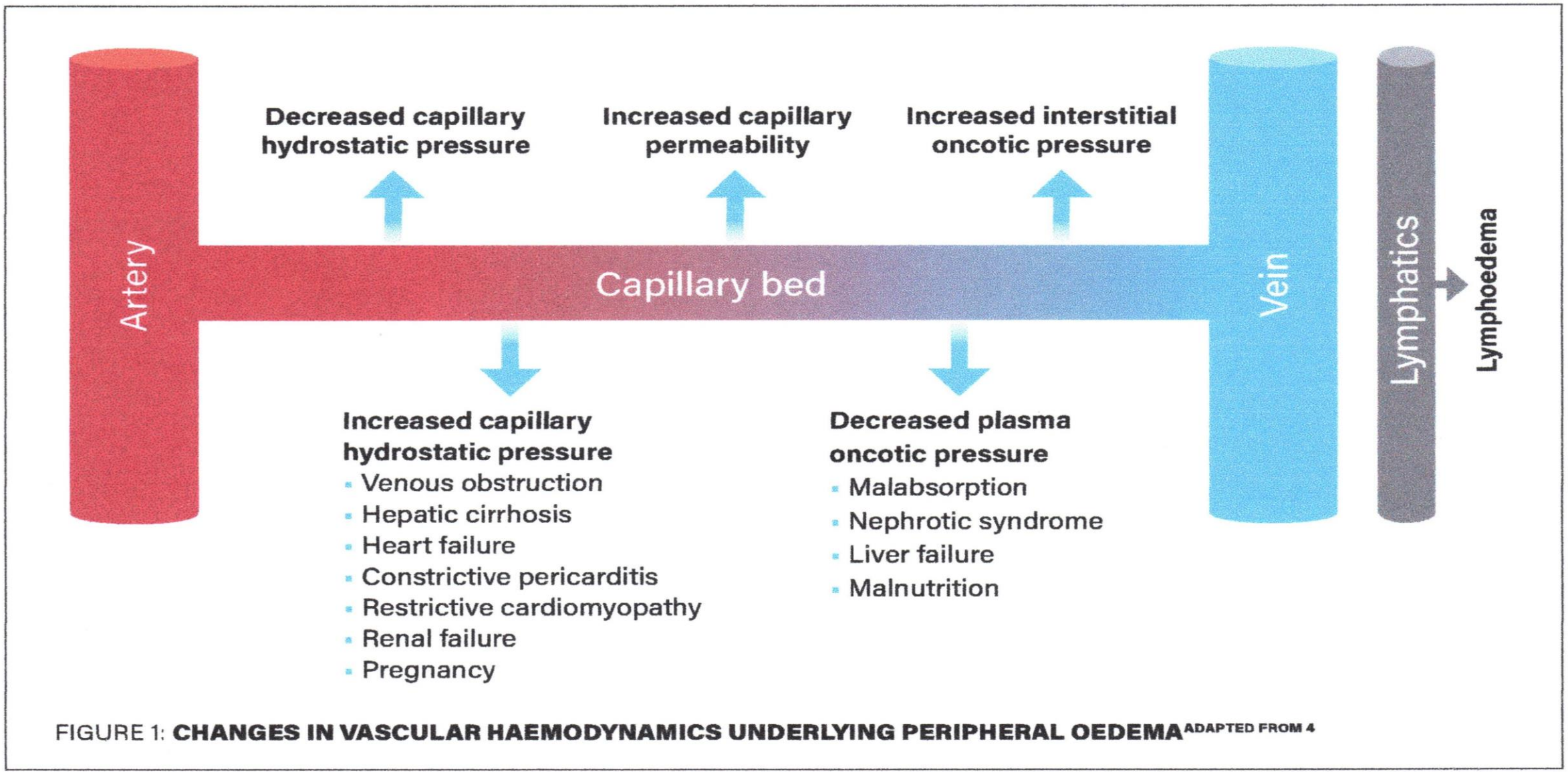

FIGURE 1: **CHANGES IN VASCULAR HAEMODYNAMICS UNDERLYING PERIPHERAL OEDEMA** ADAPTED FROM 4

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TABLE 1: **CAUSES OF PERIPHERAL OEDEMA**

Localised Oedema	Generalised Oedema
▪ Lymphoedema ▪ Lipoedema ▪ Venous incompetence ▪ Deep vein thrombosis ▪ Dermatitis ▪ Cellulitis	▪ Myxoedema ▪ Heart failure ▪ Constrictive pericarditis ▪ Restrictive cardiomyopathy ▪ Hepatic cirrhosis ▪ Nephrotic syndrome ▪ End-stage renal failure ▪ Acute renal failure ▪ Nutritional deficiency ▪ Medications

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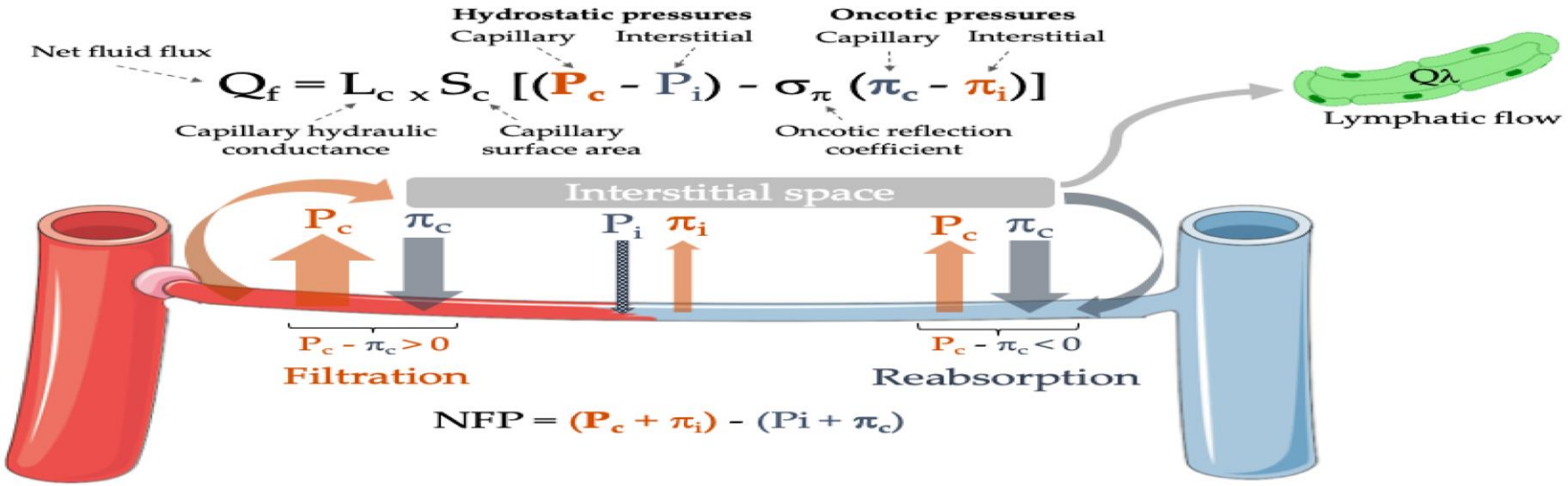

Physiology of capillary fluid exchange. Capillary hydrostatic pressure decreases along the capillary path and becomes lower than capillary oncotic pressure, which remains stable. Thus, the net filtration pressure (NFP) is positive, promoting transcapillary fluid filtration (transudation) at the arteriolar side while it is negative at the capillary outlet responsible for reabsorption of interstitial fluid into the vascular compartment.

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For most tissues, there is an imbalance between filtration and reabsorption in favour of an excess of fluid in interstitial space which is balanced by removal of interstitial fluid via the lymphatics according to its flow rate , which finally returns to the bloodstream through the thoracic duct, capillary oncotic pressure, interstitial oncotic pressure, capillary hydrostatic pressure, interstitial hydrostatic pressure, lymphatic flow, net fluid flux, capillary hydraulic conductance, capillary surface area, oncotic reflection coefficient

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Patient Comorbidities

Patient comorbidities that alter the physiology of capillary fluid exchange may also influence susceptibility to drug-induced peripheral oedema. The most striking example is diabetes, where all the forces involved in fluid balance between interstitial space and plasma can be altered. In addition to the effect of proteinuria on the capillary oncotic pressure, diabetic microangiopathy also alters the structure and function of the microvasculature.

Patient Comorbidities

This leads to increase the vascular permeability and loss of tone regulation, resulting in increased capillary filtration of fluid through the tissues.

Diabetic neuropathy can lead to lymphatic pump failure, which impedes interstitial albumin uptake and disrupts the transport of lymphatic fluid along lymphatic vessels.[34] In addition, several diseases such as diabetes and venous hypertension are associated with an altered veno-arteriolar reflex

Patient Comorbidities

In these situations, it can be assumed that the patient comorbidity burden lowers the threshold for oedema formation, so the drug may act as a trigger or aggravating factor. Drug-induced peripheral oedema can then be wrongly attributed to an underlying uncontrolled pathology (eg, heart failure). Many patients may subsequently experience a prescribing cascade that can causes harm and is costly.

Age

Age is an important determinant in peripheral oedema as aging is associated with a more precarious balance between transcapillary flow, compensatory mechanisms and lymphatic drainage capacity. This is particularly true with regard to hydrostatic oedema, where elderly subjects accumulate venous valve dysfunction[24] and tissue relaxation. A decrease in valvular function leads to reflux, causing stasis which increases capillary hydrostatic pressure and promotes oedema.

Sex

Some data report a greater incidence of peripheral oedema induced by Calcium channel blockers such as amlodipine and verapamil in women compared with men.

Several assumptions can be made to explain the effect of gender. Some authors have made the curious supposition that women are more sensitive to reporting cosmetic changes such as oedema. Another explanation could be that women in general, possibly due to chronic venous insufficiency

Finally, given that Calcium channel blocker-related oedema is concentration dependent, a more interesting possibility may be pharmacokinetic. Indeed, with an equivalent dose of verapamil or amlodipine, women obtain higher plasma concentrations than men.

TABLE 2: **MEDICATIONS AND POSSIBLE MECHANISM IN PERIPHERAL OEDEMA**

Medication	Possible Mechanism
Antidepressants—escitalopram, mirtazapine, paroxetine, venlafaxine	Arteriolar vasodilatation through 5-HT_2 receptors inhibition
Antiepileptics—carbamazepine, clobazam, valproate	Unknown
Antihypertensives—minoxidil, CCBs, α1-blockers, α2-adrenoreceptor agonists, β-blockers	Preferential precapillary arteriolar vasodilatation (minoxidil, hydralazine, CCBs), venoarteriolar reflex inhibition (CCBs), sodium retention through increased proximal tubular reabsorption in case of renal hypoperfusion (minoxidil, hydralazine) or by reactive stimulation of RAAS (α1-blockers, α2-agonists)
NSAIDs	Sodium and water retention through inhibition of PGI_2-related afferent arteriole vasodilatation and reduction of PGE_2-dependent natriuresis and aquaresis
Dopamine agonists, levodopa, MAOI-B	Arteriolar vasodilatation through peripheral D1 receptors stimulation, precapillary arteriolar vasodilatation through elevated ACE2 induced by D3 receptors stimulation, heart failure (pramipexole, bromocriptine)
Antipsychotics—clozapine, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone	Arteriolar vasodilatation through α1-adrenolytic effect and/or by 5-HT_2 receptors inhibition

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TABLE 2: **MEDICATIONS AND POSSIBLE MECHANISM IN PERIPHERAL OEDEMA**

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Antipsychotics—clozapine, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone	Arteriolar vasodilatation through α1-adrenolytic effect and/or by 5-HT_2 receptors inhibition
Gabapentinoids—gabapentin, pregabalin	Preferential precapillary arteriolar vasodilatation and inhibition of the myogenic response
Oestrogens	Increased capillary permeability, sodium and water retention
Progestins	Sodium and water retention for progestins without anti-mineralocorticoid effect
Aromatase inhibitors—anastrozole, letrozole	Sodium and water retention
SERM—tamoxifen	Sodium and water retention
GnRH agonists—gosereline, leuprolide	Sodium and water retention and through reduction of the anti-mineralocorticoid effect of progesterone
Insulin	Increased capillary permeability, arteriolar vasodilatation, sodium and water retention due to intrinsic antinatriuretic effect and through RAAS activation
Analgesics—fentanyl, hydromorphone, morphine, oxycodone, tramadol	Increased capillary permeability through nonspecific histamine releasing effects
Corticosteroids	Sodium retention through mineralocorticoid effect

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NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

Nonsteroidal anti-inflammatory drugs like ibuprofen, naproxen, Mobic, Celebrex are commonly used to treat mild to moderate pain, inflammation, and fever. Especially at higher doses of NSAIDs, prolonged use of these commonly-used drugs can cause kidney injury, which, in turn, causes oedema. However, with short-term use, NSAIDs cause salt retention. Fortunately, this type of swelling will resolve once the medication is discontinued

Peripheral oedema is not uncommon as it occurs in 2-5% of nonsteroidal anti-inflammatory drugs (NSAIDs) users, especially when patients are at risk of increasing susceptibility to the clinical effect of NSAID-induced vasoconstriction (eg, absolute volume depletion, old age). NSAID-induced peripheral oedema has both direct and indirect mechanisms that are independent on renin angiotensin aldosterone system; which they otherwise inhibit. Indeed, NSAIDs inhibit renin angiotensin aldosterone system

CORTICO STEROID MEDICINES

Corticosteroids eg. prednisone and methylprednisolone can cause sodium retention through a direct action on the kidney. This can result in fluid retention and hypertension. The effect is dependent upon the dose and duration of treatment. Moon face (a swollen, puffy, and round face) is a common side effect of steroid medications. They can also cause oedema in the abdomen (midsection) and legs

Blood pressure medications cause oedema

Calcium channel blockers (e.g., amlodipine, Diltiazem, Felodipine, Nifedipine, Verapamil) a commonly prescribed drug class to manage blood pressure, can cause oedema as a side effect.

For example, swelling is a prevalent side effect of all CCB's, and the risk of this side effect increases at higher doses. Other antihypertensive drugs, such as clonidine, hydralazine, and beta blockers, are also associated with swelling.

A classical pharmacodynamic effect of Calcium channel blockers is to induce diffuse and bilateral swelling of the feet, ankles and sometimes lower legs that worsens throughout the day and improves overnight. The peripheral oedema observed with Calcium channel blockers can differ in appearance from more traditional oedema states in that lower extremity redness, warmth and a non-blanching petechial rash can occur.

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The mechanism explaining this effect is more complex than routinely described. First, Calcium channel blockers vasodilate arterioles but not venules. This selective arteriolar vasodilatation is often described as the main cause for the increased capillary pressure observed under Calcium channel blockers . However, this cannot account for the whole effect, as venules are capacitance vessels exerting only a weak resistance to the blood flow. The second mechanism linked to the voltage-operated channel blockade itself is the alteration of blood flow autoregulation

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ANTIDEPRESSANTS

Almost all major classes of antidepressants were found to be associated with oedema. Among these drugs, trazodone, mirtazapine, and escitalopram were the most implicated. Older age and female gender were more commonly associated with oedema. Etiologically, antagonism of α1 adrenergic receptors and 5HT2A receptors, leading to vasodilation and oedema, emerged as the most prevalent mechanisms. In most cases, the oedema subsided following the discontinuation of the antidepressants. Monoamine oxidase inhibitors (MAOIs) can cause retention of fluid and swelling.

JOSEPH ET AL. Peripheral oedema associated with antidepressant use *Hum Psychopharmacol Clin Exp*. 2023;e2884.

Gabapentinoids

Gabapentinoids such as gabapentin and pregabalin 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.

Gabapentinoids cause peripheral oedema in about 2% to 16% of patients. The risk of peripheral oedema is age- and dose-related.

Doses greater than 1800mg per day of gabapentin and more than 300mg per day of pregabalin have a three-fold increased incidence of peripheral oedema

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Lymphedema

The pathophysiological mechanism of drug-induced lymphedema results from impaired lymphatic drainage that overcomes transcapillary filtration. A few drugs are involved, such as tamoxifen, taxanes (eg, paclitaxel and docetaxel). Diagnosis is made difficult by the fact that these drugs are also responsible for peripheral oedema due to increased capillary permeability (eg, taxanes, sirolimus) and that early-stage lymphedema mimics other causes of extremity swelling. As in other causes of lymphedema, transient nontender oedema occurs in newly developed drug-induced lymphedema. Over time, the skin becomes indurated with a leathery texture because of skin thickening and fibrosis.

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Conclusion

With the exception of Calcium channel blocker very little published research is available. It is essential when treating any wound patient that a full drug history is taken including prescribed, OTC’s and complimentary products to identify any potential medication that may induce peripheral oedema.

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Thank You