DEFINITION
Edema is defined as the abnormal fluid accumulation in the interstitial space that exceeds the capacity of physiological lymphatic drainage.

Pedal edema is a common presentation of various systemic and non-systemic diseases among Indian population which is always an enigma. A proper understanding of the pathophysiological basis of pedal edema and a systematic approach towards a patient can help a physician to narrow down to the right cause.

MECHANISM
Interstitial fluid space is dependent on the hydrostatic and oncotic pressure gradient across the capillaries and also the lymphatic drainage. So they are dependent on four main factors, namely-

a. Capillary permeability
b. Capillary hydrostatic pressure
c. Capillary oncotic pressure
d. Lymphatic drainage

Any derangement of one or more of these four factors which are involved in the regulation of interstitial fluid results in pedal edema.

CAUSES
Generally, causes of pedal edema can be identified on the basis of their pathophysiological mechanism.

Increased capillary permeability –
Local Causes – cellulitis (Figure 1)
Systemic Causes – allergic reactions

Increased hydrostatic pressure –
Local Causes – compartment syndrome, chronic venous insufficiency

Systemic Causes – congestive cardiac failure, renal failure, anemia, pregnancy and also pulmonary hypertension secondary to Obstructive sleep apnea syndrome.

Decreased oncotic pressure
Systemic Causes – Protein deficient states like chronic liver diseases, nephrotic syndrome, protein losing enteropathy, malabsorption syndrome can result in pedal edema.

Miscellaneous causes
Lymphatic obstruction – poor drainage of the interstitial fluid also results in pedal edema. It may be due to -

a. Primary – Congenital lymphedema which is seen at birth or before 2 years, lymphedema precox, which is common in females, before 35 years of age and lymphedema tarda which is seen after 35 years of age.

b. Secondary – Obstruction of lymphatic drainage due to tumour, trauma, radiation and infections like filariasis.

A. Lipidema – deposition of fluid in adipose tissue.

B. Idiopathic edema – In females of menstruating age idiopathic or cyclical edema is seen throughout the menstruating period. It has to be differentiated from premenstrual edema which often occurs few days prior to menstruation.

The Causes of Edema are given in Figure 2.

Fig. 1: Right leg Cellulitis with edema

Fig. 2: Algorithm for approach to pedal edema
MISCELLANEOUS

PEDAL EDEMA: INDIAN SCENARIO

Coronary Artery Heart Disease and Heart Failure

Heart failure is a major public health issue globally with a current prevalence of over 23 million worldwide. From the 1970s to 1990s, a dramatic increase in the prevalence of Heart failure and number of Heart failure hospitalizations was observed in USA. The growing prevalence of HF might reflect an aging population and improvements in the treatment of Cardiovascular diseases and Heart failure or a combination of these factors.22

India is going through an epidemiologic transition whereby the burden of communicable diseases have declined slowly, but that of non-communicable diseases (NCD) has risen rapidly, thus leading to a dual burden. Reliable estimates of heart failure are lacking in India because of the absence of a surveillance programme to track incidence, prevalence, outcomes and key causes of heart failure. Based on disease-specific estimates, the prevalence of heart failure in India due to coronary heart disease, hypertension, obesity and rheumatic heart disease ranges from 1.3 to 4.6 million, with an annual incidence of around 0.5 to 1.8 million.23

Rheumatic Heart Disease and Heart Failure

Hospital based data between 1945 and 1963 indicate that anywhere between 20% and 50% of all hospital admissions for cardiac patients were for RHD. ICMR has conducted three school-based surveys on prevalence of RHD among children aged between 5 to 14 years over a 40-year period between 1970 and 2010. In the first study (1972-1975), the prevalence of RHD was found to be 5.3/1000. In the second study (1984-1987), the overall prevalence of RHD was ranged 2.9/1000. In the third study which was the largest one, the overall prevalence was 0.9/1000. This data clearly shows that there is a steady decline in the prevalence of RHD in India along with a decline in the incidence of Heart failure due to RHD.26

Chronic Liver Disease

In India, Hepatitis B and Hepatitis C Virus infections were the leading cause of Chronic Liver Disease (CLD) in the past. But, alcohol has fast caught up, especially after 2007 and it is the leading cause of CLD related morbidity and mortality burden at present. A recent publication highlighting the “alcohol situation in India” strongly supports the above statement. This article highlighted that about 21% of adult men and 2% of adult women drink alcohol, of them 20% are “problem” drinkers. The number of drinkers in young age has increased from 2 to 14% in past 15 years. From1979 to 2005 CLD mortality has doubled and two-third of which is due to alcohol.27

Chronic Venous Insufficiency

On a global perspective 1 out of 5 people suffer from Chronic Venous Insufficiency (CVI). This can be mainly attributed to occupation, lifestyle changes, environmental factors, a familial tendency and post-partum period. In India, incidence of CVI remains an iceberg phenomenon, since patients with CVI seek treatment very late.29,30

Filariasis

In India, the incidence of microfilarial infection has decreased from 1.24% to 0.26% over a period of 11 years from 2004 to 2015 along with a decrease in the incidence of lymphedema (Elephantiasis).31

The above data clearly shows that there is changing pattern in the etiology of pedal edema from communicable diseases like HBV, HCV and Filariasis to non-communicable diseases like CHD, Alcoholic Liver Disease, CKD due to Diabetes Mellitus, Systemic Hypertension etc..

EVALUATION OF PEDAL EDEMA

History

A detailed history is the most important component in the evaluation of pedal edema as it often gives a clear perspective which can pin point the underlying cause (Figure 3).

I. SITE AND DISTRIBUTION – Whether the pedal edema is unilateral or bilateral. Unilateral edema results mainly due to local causes like Deep vein thrombosis (DVT), cellulitis, compartment syndrome and filarial lymphatic obstruction. Bilateral pedal edema is mainly due to systemic causes like congestive cardiac failure, anemia, chronic kidney disease and chronic liver disease.11,12

II. DURATION OF ILLNESS – Short duration of
the illness indicates an acute cause like Cellulitis, DVT, Compartment syndrome etc., which usually occurs in 72 hours.9,10

III. ASSOCIATION WITH PAIN – Conditions like Deep Vein thrombosis and cellulitis are generally painful whereas edema due to Heart failure, hypoproteinemia and lymphedema are painless. A dull aching type of pain is seen in chronic venous insufficiency.9

IV. VARIABILITY OF EDEMA – Venous edema due to congestive cardiac failure and venous insufficiency is aggravated by standing and improves with overnight limb elevation during sleep. Idiopathic edema which is seen in females increases throughout the day during upright posture.

V. HISTORY OF SYSTEMIC ILLNESS – Symptoms of systemic diseases like exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea and chest pain point to cardiac failure; history of oliguria and puffiness of face suggest renal etiology; long term alcohol consumption, yellowish discoloration of eyes and urine and abdominal distension points to cirrhosis of liver; symptoms of endocrine disorders like hypothyroidism are often missed. Similar history about all other systemic causes of pedal edema should be elicited in detail. Patients who are bed ridden for a prolonged period of time have dependent edema over the sacral area.

VI. HISTORY OF DRUG INTAKE – Drugs like calcium channel blockers, NSAIDs and steroids can cause pedal edema. Around 50% of patients taking calcium channel blockers and 5% of patients taking NSAIDs complain of pedal edema.13,14 (Table 1)

VII. HISTORY OF TRAUMA AND RADIATION – Trauma and radiation can cause cellulitis and compartment syndrome leading to pedal edema which may be unilateral or bilateral. Long term radiation can also cause lymphedema in some patients.

VIII. MISCELLANEOUS CAUSES – Obstructive sleep apnea can also cause pedal edema due to right ventricular failure. However it is always a diagnosis of exclusion.

CLINICAL EXAMINATION: A thorough and meticulous physical examination should be carried out in all the patients with pedal edema which along with a detailed history helps the physician to make a fairly accurate diagnosis.

i. Local examination –

I. Distribution - Identify whether it is unilateral (usually local causes) or bilateral (predominantly systemic causes, sometimes local).

II. Site – Bony prominences like medial malleolus and medial surface of tibia along with the dorsum of foot has to be examined thoroughly. Dorsum of foot is not involved in lipidema which usually involves the medial malleolus area of foot.

III. Tenderness – Deep vein thrombosis, cellulitis, lipidema and compartment syndrome are generally tender. However, lymphedema and edema due to systemic diseases are painless.

IV. Pitting edema – Except in cases of edema due to lymphatic obstruction and myxedema, most of the other diseases cause pitting pedal edema. However, in early stages of lymphedema, it is usually pitting13 (Figure 4).

V. Skin changes
a. Myxedema – Dry, coarse and thick skin is noted
b. Chronic venous insufficiency – Hemosiderin deposition causes brawny skin commonly over the medial malleolus. Often varicose veins are seen on the medial side of the leg.13

c. Chronic lymphedema – hyperkeratotic and papillomatous skin with induration which is known as lymphostatic verrucosis (elephantiasis)4

Table 1: Drugs Causing Pedal Edema

<table>
<thead>
<tr>
<th>Drug classification</th>
<th>Drug</th>
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<tr>
<td>Anti – hypertensives</td>
<td>Calcium channel blockers</td>
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<td></td>
<td>Beta blockers</td>
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<td>Methyl dopa</td>
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<td>Testosterone</td>
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<td>Anti - depressants</td>
<td>MAO inhibitors</td>
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<td>NSAIDs</td>
<td>Ibuprofen</td>
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<td></td>
<td>Diclofenac</td>
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<tr>
<td>Oral hypoglycemics</td>
<td>Rosiglitazone</td>
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<td></td>
<td>Pioglitazone</td>
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MISCELLANEOUS

(Figure 5). Kaposi-stemmer sign - It is the inability to pinch the skin on the dorsum of the foot near the second toe.

ii. Systemic examination –
I. Congestive cardiac failure – Elevated jugular venous pressure, third heart sound and crepitations over the lung bases.
II. Decompensated liver disease – Jaundice, ascites, splenomegaly, gynaecomastia and spider naevi.
III. Chronic kidney disease – Anemia, dry skin, uremic breath.
IV. Hypothyroidism – Bradycardia, skin changes like dry skin and sparse hair, hoarseness of voice.

INVESTIGATIONS
A set of baseline investigations has to be done to pin point the underlying diagnosis in a cases of pedal edema along with special investigations if indicated.

a. Complete blood count – helps to diagnose anemia and also gives some clues regarding the cause anemia.
b. Urine analysis, renal function test & USG KUB – Help to diagnose chronic kidney disease & nephrotic syndrome.
c. Liver function test including serum protein – Diseases like cirrhosis, nephrotic syndrome, protein losing enteropathy and malnutrition can be detected by these tests.
d. Serum lipid profile – Nephrotic syndrome is associated with hyperlipidemia. Dyslipidemia is also a risk factor for coronary heart disease.
e. Chest X ray, ECG and Brain natriuretic peptide – These tests are used for identifying heart failure. Brain natriuretic peptide has sensitivity of 90% and specificity of 76% in predicting heart failure.
f. D-dimer estimation – In acute cases of pedal edema, it can be used to identify deep vein thrombosis. However, in patients with elevated D-dimer levels, additional imaging investigations like Doppler study have to be carried out for the definitive diagnosis of DVT.
g. Imaging studies –
1. Doppler study – it is the imaging study of choice with a high specificity and sensitivity for diagnosing Deep vein thrombosis and chronic venous insufficiency.
2. Lympho scintigraphy – Lymphedema can be identified using a radio-nucleotide tracer which is injected into the first web space and the flow of the lymph is monitored using a gamma camera. This gives an indirect evidence of lymphatic obstruction.
3. Echocardiography – It is used for the assessment of left ventricular function in patients with congestive heart failure. It can also measure the pulmonary artery pressure and helps in diagnosing pulmonary hypertension in conditions like cor pulmonale and Obstructive sleep apnea syndrome.

MANAGEMENT OF PEDAL EDEMA
Treatment of pedal edema widely differs across the spectrum of etiology.

A. Venous insufficiency – Initial stages of venous insufficiency resolve easily with limb elevation. However in chronic states it needs high knee compression stockings. Before using stockings peripheral vascular disease has to be ruled out by ankle brachial index or arterial doppler as they may aggravate the underlying condition. Patients who are refractory to treatment with stockings and who are contraindicated for stockings need pneumatic compression devices. Diuretics are of no use and often avoided as they can cause metabolic derangements. Skin care with topical steroids and emollients should be used to avoid excoriation and ulceration.

Congestive heart failure and chronic liver disease – Respond to fluid restriction, salt restriction and limb elevation in the early stages and diuretics like frusemide and spironolactone can be used for patients who do not respond to the above measures. Albumin infusion can also be used to correct the
hypoalbuminemia in liver failure which provides temporary relief.

C. Chronic renal failure – Fluid restriction and salt restriction are the initial line of management of renal failure. In refractory cases, loop diuretics like frusemide or torsemide can be given. Aldosterone antagonist are contraindicated because of risk of developing life threatening hyperkalemia.

D. Obstructive sleep apnea – Weight reduction and continuous positive pressure ventilation helps in reducing pulmonary hypertension and improving edema.

E. Lymphedema – Initially treated with manual massaging. Compressive bandage and stockings can also be used. Later, Intermittent pneumatic compression devices are used. In refractory cases of lymphedema, surgical procedures like bypass surgery and debulking can be done. Diuretics are of no use in these patients.

F. Deep vein thrombosis – In chronic bed ridden patients, compression devices like bandages and stockings can prevent DVT. DVT is treated with early initiation anticoagulant therapy using low molecular weight heparin which is followed by oral anticoagulants.

G. Lipidema – No effective treatment is available. Weight loss is also of little use.

H. Idiopathic edema – Responds to treatment with aldosterone antagonist like spironolactone.

REFERENCES