Idiopathic edema

Author: Richard H Sterns, MD
Section Editor: Michael Emmett, MD
Deputy Editor: John P Forman, MD, MSc

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Jun 2019. | **This topic last updated:** Nov 14, 2017.

INTRODUCTION

Idiopathic edema is a syndrome of fluid retention with swelling of the face, hands, trunk, and limbs, occurring in premenopausal women in the absence of cardiac, hepatic, or renal disease [1-4]. Diabetes, obesity and emotional problems (including depression and neurotic symptoms) are commonly part of this syndrome [5,6]. There is also an association with purging behaviors (use of diuretics, laxatives, or vomiting) to achieve weight loss, which has led some authors to question whether idiopathic edema is truly an independent entity [4].

PATHOGENESIS

Three major theories, each of which may apply to some patients, have been proposed to explain the fluid retention in idiopathic edema: capillary leak; refeeding; and diuretic-induced edema.

Capillary leak — Many women with idiopathic edema have an abnormal response to assumption of the upright posture. Normal subjects develop a mild degree of plasma volume depletion in this setting due to pooling of extracellular fluid in the lower extremities. As a result, there is a fall in urinary sodium excretion [7] and a daytime weight gain that averages 0.5 to 1.5 kg [1,2]. In comparison, women with idiopathic edema lose much more fluid from the vascular space with standing [8], leading to often marked elevations in the release of the "hypovolemic" hormones renin, norepinephrine, and ADH, and to a larger morning-to-evening weight gain that can exceed 5 kg in severe cases [1-3].

These observations have led to the suggestion that idiopathic edema may represent a capillary leak syndrome, in which increased capillary permeability favors the movement of fluid out of the vascular space, a response that is exaggerated by gravity when standing [1]. This primary tendency to plasma volume depletion also explains why the jugular venous pressure is in the low-

normal range in idiopathic edema and why pulmonary edema does not occur, even in the presence of marked peripheral edema. (See "Idiopathic systemic capillary leak syndrome".)

The factors responsible for fluid leakage out of the capillaries are not well understood: either altered capillary hemodynamics or, in selected cases, primary capillary injury could be responsible [9]. It is possible, for example, that dilatation of the precapillary sphincter plays a central role by permitting more of the systemic pressure to be transmitted to the capillary, thereby increasing the capillary hydraulic pressure. Such a response could be humorally mediated. Women with idiopathic edema often have impaired hypothalamic function, resulting in abnormal release of prolactin, luteinizing hormone, and perhaps other hormones [10].

Decreased release of dopamine has also been demonstrated in some patients [1,11]. Dopamine deficiency could account for edema formation in several ways: by impairing the regulation of hypothalamic hormone release; by altering capillary hemodynamics directly; and by reducing sodium excretion, since dopamine is normally a natriuretic hormone (see "Renal actions of dopamine").

Refeeding — Women with idiopathic edema are typically very conscious of their weight and may drastically cut down on food intake for days at a time in an effort to lose weight. The subsequent end of this fast can lead to rapid weight gain via the phenomenon of refeeding edema [12]. Increased release of insulin and possibly activation of the renin-angiotensin-aldosterone system may contribute in this setting [12]. Insulin can acutely promote sodium retention both by stimulating tubular reabsorption and by inducing hypokalemia via the movement of extracellular potassium into the cells [13,14]. (See "Hypokalemia-induced renal dysfunction".)

In some patients with idiopathic edema, extremely large diurnal weight gains occur without a decrease in the serum sodium concentration; this observation can be explained by binging after a period of fasting (and/or purging). Some have questioned whether surreptitious continuation of such behaviors might have complicated some investigative studies in this field and have questioned whether idiopathic edema is, in fact, a manifestation of an eating disorder [4,15]. A study of female college students responding to a computerized self-report questionnaire found a strong association between responses characteristic of abnormal eating attitudes and behaviors and symptoms of idiopathic edema [16].

Diuretic-induced edema — Idiopathic edema also may be paradoxically induced by the chronic administration of diuretics [12,17]. According to this hypothesis, patients are initially begun on a diuretic for a minor degree of fluid retention. As therapy is continued, persistent diuretic-induced hypovolemia results in the activation of sodium-retaining mechanisms, particularly the renin-angiotensin-aldosterone system. If the diuretic is then stopped, the patient may be unable to acutely shut off this hormonal adaptation, resulting in rapid edema formation and the mistaken assumption that chronic diuretic therapy is indicated. If, however, the patient is maintained without

diuretics for one to three weeks, a spontaneous diuresis will frequently ensue with resolution of the edema [12,17].

A somewhat similar sequence has been described in elderly patients treated with a diuretic solely for ankle edema [18]. Seventy five percent of such patients were able to discontinue the diuretic without persistent recurrence of edema. However, transient rebound edema was common and, as in the above studies in idiopathic edema, spontaneously resolved within three weeks.

The frequency with which diuretics are responsible for idiopathic edema is uncertain. Some investigators have proposed that most cases are diuretic induced [12,17], while others have found that most patients have no history or signs (volume depletion, hypokalemia, positive urine assay) of diuretic use [19].

Some and perhaps many patients who are treated with very high doses of loop diuretics for a prolonged period develop nephrocalcinosis. This issue was addressed in a review of 18 consecutive adults who were treated with furosemide for 3 to 25 years because of weight gain or idiopathic edema [20]. Nephrocalcinosis was detected on renal ultrasonography in 15 of the patients (all but one were women). The mean dose was 538 mg of furosemide per day (range 120 to 2800 mg/day) compared to 40 to 80 mg/day in the three patients without nephrocalcinosis. (See "Nephrocalcinosis".)

Other causes — A number of other possible underlying causes of idiopathic edema have been evaluated. These include disorders involving antidiuretic hormone, atrial natriuretic factor, dopamine, the thyroid gland, and the renin-aldosterone system [4]. There is little evidence for a role for any of these factors in the pathogenesis of this disorder.

DIAGNOSIS

The diagnosis of idiopathic edema is one of exclusion and should only be considered when plasma albumin concentration and jugular venous pressure are low-normal and when there is no evidence of cardiac, hepatic, or renal disease. Idiopathic edema should also be differentiated from premenstrual edema. The latter disorder occurs in many women; it is mild and self-limited, with a diuresis beginning with or shortly after the onset of menses. The fluid retention in this setting is thought to be humorally mediated, as estrogens or possibly prolactin may be responsible for the fluid retention.

Some women are already receiving diuretic therapy at the initial evaluation by a new clinician, sometimes in massive doses that can exceed 600 mg of furosemide per day [21]. As a result, hypokalemia is a common problem with the plasma potassium concentration in severe cases being persistently below 3 mEq/L. Persistent marked hypokalemia and mild hypovolemia can lead to two potential complications: rhabdomyolysis; and chronic renal insufficiency that, on renal biopsy, is characterized by renal cysts, prominent tubulointerstitial scarring and atrophy, and by

intimal thickening of the interlobular arteries [21,22]. Discontinuation of diuretic therapy generally leads to at least partial recovery of renal function [21].

TREATMENT

Since diuretic-induced edema appears to be operative in some patients, initial therapy should consist of a low-sodium diet and cessation of diuretic therapy for three to four weeks [12,17]. The patient should be advised that this will initially lead to weight gain and reassured that diuretics can be always be reinstituted if a spontaneous diuresis does not ensue [4]. If it becomes evident that a diuretic is required, the lowest effective dose should be used and given in the early evening since the edema primarily accumulates during the daytime when the patient is erect [2].

In patients not taking diuretics or those who fail to respond to diuretic withdrawal, it has been suggested that a diet restricted in sodium and carbohydrate (approximately 90 g/day) leads to resolution of edema in many cases [19]. It is presumed that this effect is the reverse of the sodium retention seen with refeeding.

Patients who are resistant to this conservative regimen are often difficult to treat effectively. High-dose loop diuretic therapy should be avoided because of its association with acute and chronic kidney injury [21]. An alternative that has been effective in some cases is blockade of the renin-angiotensin system with an angiotensin-converting enzyme (ACE) inhibitor [8,23]. Minimizing the degree of secondary hyperaldosteronism (by decreasing angiotensin II-mediated aldosterone release) may diminish the quantity of fluid retained during the day. It does not, however, prevent the capillary leak or plasma volume depletion. As a result, ACE inhibitors often lower the systemic blood pressure by 5 to 10 mmHg, producing symptoms of hypotension in some patients [23]

Other modalities — Other modalities have been tried in refractory idiopathic edema. Selected patients have responded to therapy aimed at reversing a possible dopamine deficiency by the administration of the dopamine agonist bromocriptine or a carbidopa-levodopa combination [1,11,24]. The efficacy of these agents, however, remains unproven and their use may be associated with unacceptable side effects.

Increasing sympathetic activity with low-dose amphetamines or preferably the sympathetic agonist ephedrine (15 to 60 mg TID) also may be beneficial [2,25,26]. These drugs may act by constricting the precapillary sphincter, thereby lowering the capillary hydraulic pressure and retarding fluid movement out of the capillary. Ephedrine has been given successfully with an ACE inhibitor [26] and has also been used to treat the rare syndrome of insulin-induced edema in patients with poorly controlled diabetes mellitus [27,28]. Side effects can be minimized by using lower ephedrine doses.

Metformin has been tested as a treatment for idiopathic edema, based upon evidence that it alters capillary permeability. In two small, uncontrolled trials of women, metformin (500 mg orally twice

daily) successfully eliminated or reduced idiopathic edema in nearly all patients [29,30].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Fluid and electrolyte disorders".)

SUMMARY AND RECOMMENDATIONS

- Idiopathic edema is a syndrome of real or perceived fluid retention with swelling of the face, hands, trunk, and limbs, occurring in premenopausal women in the absence of cardiac, hepatic, or renal disease. (See 'Introduction' above.)
- Three major theories have been proposed to explain the fluid retention in idiopathic edema: capillary leak; refeeding; and diuretic-induced edema. (See 'Capillary leak' above and 'Refeeding' above and 'Diuretic-induced edema' above.)
- The diagnosis of idiopathic edema is one of exclusion and should only be considered when the plasma albumin concentration and jugular venous pressure are normal, and when there is no evidence of cardiac, hepatic, or renal disease. Idiopathic edema should also be differentiated from premenstrual edema. (See 'Diagnosis' above.)
- Some women are already receiving diuretic therapy at the initial evaluation by a new clinician, sometimes in massive doses that can exceed 600 mg of furosemide per day. As a result, hypokalemia is a common problem with the plasma potassium concentration in severe cases being persistently below 3 mEq/L. (See 'Diagnosis' above.)
- Since diuretic-induced edema appears to be operative in some patients, initial therapy should consist of a low-sodium diet and cessation of diuretic therapy for three to four weeks. (See 'Treatment' above.)
- In patients not taking diuretics or those who fail to respond to diuretic withdrawal, it has been suggested that a diet restricted in both sodium and carbohydrate (approximately 90 g/day) leads to resolution of edema in many cases. (See 'Treatment' above.)
- Patients who are resistant to this conservative regimen are often difficult to treat effectively. High-dose loop diuretic therapy should be avoided because of its association with acute and chronic kidney injury. An alternative that has been effective in some cases is blockade of the renin-angiotensin system with an angiotensin-converting enzyme (ACE) inhibitor. (See 'Treatment' above.)

- In refractory idiopathic edema, selected patients respond to the dopamine agonist bromocriptine or a carbidopa-levodopa combination. Increasing sympathetic activity with low-dose amphetamines or preferably the sympathetic agonist ephedrine (15 to 60 mg TID) also may be beneficial. (See 'Other modalities' above.)

REFERENCES

1. Badr KF. Idiopathic edema. In: Contemporary Issues in Nephrology (Body Fluid Homeostasis), Brenner BM, Stein JH, Churchill Livingstone, New York 1987. Vol 16.
2. Streeten DH. Idiopathic edema: pathogenesis, clinical features, and treatment. Metabolism 1978; 27:353.
3. Edwards OM, Bayliss RI. Idiopathic oedema of women. A clinical and investigative study. Q J Med 1976; 45:125.
4. Kay A, Davis CL. Idiopathic edema. Am J Kidney Dis 1999; 34:405.
5. Pelosi AJ, Sykes RA, Lough JR, et al. A psychiatric study of idiopathic oedema. Lancet 1986; 2:999.
6. Dunnigan MG, Henderson JB, Hole D, Pelosi AJ. Unexplained swelling symptoms in women (idiopathic oedema) comprise one component of a common polysymptomatic syndrome. QJM 2004; 97:755.
7. EPSTEIN FH, GOODYER AV, LAWRASON FD, RELMAN AS. Studies of the antidiuresis of quiet standing: the importance of changes in plasma volume and glomerular filtration rate. J Clin Invest 1951; 30:63.
8. Docci D, Turci F, Salvi G. Therapeutic response of idiopathic edema to captopril. Nephron 1983; 34:198.
9. Coleman M, Horwith M, Brown JL. Idiopathic edema. Studies demonstrating protein-leaking angiopathy. Am J Med 1970; 49:106.
10. Young JB, Brownjohn AM, Chapman C, Lee MR. Evidence for a hypothalamic disturbance in cyclical oedema. Br Med J (Clin Res Ed) 1983; 286:1691.
11. Sowers J, Catania R, Paris J, Tuck M. Effects of bromocriptine on renin, aldosterone, and prolactin responses to posture and metoclopramide in idiopathic edema: possible

therapeutic approach. J Clin Endocrinol Metab 1982; 54:510.

12. Idiopathic edema: role of diuretic abuse. Kidney Int 1981; 19:881.

13. Baum M. Insulin stimulates volume absorption in the rabbit proximal convoluted tubule. J Clin Invest 1987; 79:1104.

14. Friedberg CE, van Buren M, Bijlsma JA, Koomans HA. Insulin increases sodium reabsorption in diluting segment in humans: evidence for indirect mediation through hypokalemia. Kidney Int 1991; 40:251.

15. Mitchell JE, Pomeroy C, Seppala M, Huber M. Pseudo-Bartter's syndrome, diuretic abuse, idiopathic edema, and eating disorders. Int J Eat Disord 1988; 7:225.

16. Bihun JA, McSherry J, Marciano D. Idiopathic edema and eating disorders: evidence for an association. Int J Eat Disord 1993; 14:197.

17. MacGregor GA, Markandu ND, Roulston JE, et al. Is "idiopathic" edema idiopathic? Lancet 1979; 1:397.

18. de Jonge JW, Knottnerus JA, van Zutphen WM, et al. Short term effect of withdrawal of diuretic drugs prescribed for ankle oedema. BMJ 1994; 308:511.

19. Pelosi AJ, Czapla K, Duncan A, et al. The role of diuretics in the aetiology of idiopathic oedema. QJM 1995; 88:49.

20. Kim YG, Kim B, Kim MK, et al. Medullary nephrocalcinosis associated with long-term furosemide abuse in adults. Nephrol Dial Transplant 2001; 16:2303.

21. Shichiri M, Shiigai T, Takeuchi J. Long-term furosemide treatment in idiopathic edema. Arch Intern Med 1984; 144:2161.

22. Riemenschneider T, Bohle A. Morphologic aspects of low-potassium and low-sodium nephropathy. Clin Nephrol 1983; 19:271.

23. Suzuki H, Fujimaki M, Nakane H, et al. Effect of the angiotensin converting enzyme inhibitor, captopril (SQ14,225), on orthostatic sodium and water retention in patients with idiopathic edema. Nephron 1985; 39:244.

24. Edwards OM, Dent RG. Idiopathic edema. Lancet 1979; 1:1188.

25. SPELLER PJ, STREETEN DH. MECHANISM OF THE DIURETIC ACTION OF D-AMPHETAMINE. Metabolism 1964; 13:453.

26. Edwards BD, Hudson WA. A novel treatment for idiopathic oedema of women. Nephron 1991; 58:369.

27. Hopkins DF, Cotton SJ, Williams G. Effective treatment of insulin-induced edema using ephedrine. Diabetes Care 1993; 16:1026.

28. Kalambokis GN, Tsatsoulis AA, Tsianos EV. The edematogenic properties of insulin. Am J Kidney Dis 2004; 44:575.

29. Soudet S, Lambert M, Lefèvre G, et al. Long term use of metformin in idiopathic cyclic edema, report of thirteen cases and review of the literature. Pharmacol Res 2017; 119:237.

30. Valensi P, Behar A, Andre P, et al. The effects of metformin on the capillary permeability to albumin in women patients with cyclic edema. Angiology 1995; 46:401.

Topic 2349 Version 10.0

Contributor Disclosures

Richard H Sterns, MD Nothing to disclose **Michael Emmett, MD** Consultant/Advisory Boards: AstraZeneca (Lokelma - Zirconium Silicate). **John P Forman, MD, MSc** Nothing to disclose

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy