Insulin oedema

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Summary: A 35 year old markedly underweight woman presented with uncontrolled diabetes. Following insulin therapy she developed gross fluid retention with extensive peripheral oedema, bilateral pleural effusions and weight gain of 18.8 kg in 22 days, accompanied by a fall in plasma albumin. She responded well to treatment with diuretics and salt-poor albumin, losing 10.3 kg in 6 days without recurrence of oedema. Severe insulin oedema is an uncommon complication of insulin therapy and may be due to effects of insulin on both vascular permeability and the renal tubule.

Introduction

Extensive oedema formation is an uncommon complication of insulin therapy and has been termed 'insulin oedema' (Leifer, 1928). It must be differentiated from other causes of oedema such as cardiac or renal disease, which may themselves arise independently or as a complication of the diabetic state. We report the case of a markedly underweight woman newly presenting with diabetes in whom extensive fluid retention accompanied by large bilateral pleural effusions followed the initiation of insulin therapy.

Case report

A 35 year old woman presented with a 2-year history of general malaise, weight loss of 13 kg and amenorrhoea. Increased thirst, polyuria and polydipsia had been present for 3 months and a painful swelling of the left foot for 6 weeks. Both maternal grandparents had diabetes mellitus. Examination revealed a markedly underweight, mildly dehydrated woman (weight 38.2 kg, height 1.727 m, body mass index 12.8) with several areas of necrobiosis lipoidica on her shins. She was afebrile and had a sinus tachycardia of 120/min, with blood pressure of 110/80 mm Hg. There was a glove and stocking neuropathy for all modalities of sensation extending to the wrists and knees, and ophthalmoscopy showed a severe background retinopathy. Initial investigations were as follows: plasma glucose 29.4 mmol/l; venous pH 7.35; plasma ketones (ketostix, Ames) ++; urine glucose and ketones + + +. Haemoglobin 10.9 g/dl; haematocrit 0.348; white cell count $13.9 \times 10^9/l$ (neutrophil leucocytosis);

creatinine (64 $\mu\text{mol/l}$), urea (6.3 mmol/l) and electrolytes normal. Plasma albumin was 34 g/l (normal range 35–50), total protein 69 g/l and liver function tests normal. A midstream urine sample was without proteinuria, and chest X-ray and electrocardiograph were normal. Islet cell antibodies were positive, cholesterol, triglycerides, iron, iron binding capacity, red cell folate, transketolase (84 IU/l), and transketolase plus thiamine pyrophosphate (105 IU/l), all normal. There were no muscle fibres or fat globules in the stool.

She was initially treated with an intravenous infusion of insulin and normal saline (3 litres in 24 hours). Treatment was continued with twice daily Actrapid and Insulatard insulin totalling 40 units/day, increasing over the next 3 weeks to a maximum of 110 units/day to maintain blood glucose between 8 and 16 mmol/l (Figure 1). Mild bilateral pitting ankle oedema was first noted on day 13 and progressed over the next week. By day 22 she complained of breathlessness on exertion and had marked fluid retention with elevated jugular venous pressure, tender hepatomegaly, gallop rhythm, extensive peripheral pitting oedema, facial puffiness and large bilateral pleural effusions (Figure 2). Echocardiography showed good left ventricular function and no cardiac abnormality other than a small pericardial effusion. A diagnostic pleural tap showed a protein content of 21 g/l. She had gained 18.8 kg in weight since admission and plasma albumin had fallen to 25 g/l. She was treated with frusemide and salt-poor albumin over the next 2 days with a good diuresis and rise in albumin, but regained weight on discontinuing this therapy. Re-introduction of diuretic and albumin resulted in a further diuresis with weight loss of 10.3 kg in 6 days. The body mass index was now 15.7. Frusemide was discontinued on day 32, by which time the fluid retention had completely resolved and did not recur throughout her admission. Repeated urinary protein estimations were

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Figure 1 Body weight, plasma albumin and insulin dose following admission.

<100 mg/l, microscopy was negative for cells and casts and she remained normotensive with normal plasma urea and creatinine throughout her admission.

Six months after admission she was well, had gained weight and menses had resumed. Her diabetes was well controlled and there had been no recurrence of the oedema.

Discussion

'Although I am certain that oedema develops frequently in diabetic patients treated with insulin, very few cases have been reported in the literature' wrote Leifer

Figure 2 Chest X-ray at day 22 of admission, showing bilateral pleural effusions and peri-hilar shadowing.

in 1928. More than 50 years later, however, only a few further reports of marked insulin oedema in white subjects have appeared (Griep, 1955; Kirtley, 1955; Deckert, 1958; Marthedal *et al.*, 1982), prompting the recent comment that 'clearly it must be a rare phenomenon in Britain' (Bleach *et al.*, 1979). Insulin oedema has also been reported in two series from East Africa (Haddock, 1964; Shaper, 1966), in which 22 of 607 (3.7%) newly presenting black diabetic patients showed some degree of oedema formation. In most of these cases, the oedema followed soon after the initiation of insulin therapy or a substantial increase in the insulin dose. There appears to be no sex difference in incidence, but many of the cases were substantially underweight. The extent of the oedema varied from marked ankle oedema to overt cardiac failure with ascites or, in our patient, pleural effusions, and was unrelated to the severity of ketosis which was often of only mild degree. Diuretic therapy or salt restriction were used to control the oedema in the short term, and there was no tendency for the oedema to persist or recur after the acute episode. Less dramatic fluid retention, manifest as mild to moderate ankle swelling, may also follow the introduction of insulin or increased insulin dose, and is seen more frequently in clinical practice (Saudek *et al.*, 1974; Lawrence & Dunnigan, 1979) though its incidence has not been well assessed.

The pathogenesis of oedema formation on treatment of uncontrolled diabetes is unknown, though a number of findings suggest the involvement of insulin. Severe acute oedema has been reported only in insulin-treated diabetic patients, usually soon after its introduction, and a common feature is of a relatively high insulin dose (50–144 units/day), particularly in

relation to the low body weight. Peripheral oedema is associated with chronic insulin overtreatment in young diabetic subjects (Rosenbloom & Giordano, 1977), and may also occur in young or middle-aged insulin-treated diabetic women (Lawrence & Dunigan, 1979). Increased endogenous plasma insulin levels are associated with moderate fluid retention both in 'idiopathic oedema' (Shaw *et al.*, 1968) and in the 'refeeding oedema' accompanying carbohydrate ingestion after starvation (Kolanowski *et al.*, 1972), which may progress to frank cardiac failure and pulmonary oedema in severely malnourished children (Patrick, 1977). The apparently increased incidence of insulin oedema in Africa may thus be due to the more common occurrence of under-nutrition, which may also have been important in our patient.

At least two possible mechanisms to produce fluid retention after insulin treatment exist. Sodium retention in the treatment of diabetic keto-acidosis with preceding salt depletion has long been recognized (Nabarro *et al.*, 1952), and may largely explain the moderate fluid retention encountered in this situation. Sodium retention may also occur during insulin treatment of non-ketoacidotic diabetic patients, even in the absence of salt depletion (Saudek *et al.*, 1974). Insulin has a direct sodium-retaining effect on the kidney in both man and experimental animals (DeFronzo *et al.*, 1975; Rostand *et al.*, 1980), most marked in diabetic animals with preceding insulin deficiency and independent of changes in renal blood flow or the renin-aldosterone axis. Insulin oedema may thus be at least partly secondary to sodium retention resulting from a direct action of insulin on the renal tubule, and leading to an expansion of interstitial and plasma volumes.

A second possible mechanism is an increase in vascular permeability (Bleach *et al.*, 1979). Insulin increases the permeability of subdermal vessels in response to injected irritants in both normal and diabetic rats (Garcia-Leme *et al.*, 1973; Goth *et al.*, 1957). Endothelial junctions are narrowed in the insulin deficient animals and this change is corrected after insulin treatment (Garcia-Leme *et al.*, 1974). In diabetic men, intravenous injection of insulin leads to

a marked reduction in the intravascular pool of albumin and so plasma volume (Gundersen & Christensen, 1977). Increased vascular permeability in our subject is suggested by the relatively high protein content of the pleural effusion in relation to the low plasma albumin, in the absence of infection. The low albumin might have reflected a dilutional effect, failure of hepatic synthesis of albumin, or its increased loss other than via the kidney, as by increased degradation. After albumin infusion, plasma levels rose but soon fell rapidly despite continued diuresis and weight loss, thus excluding the first two possibilities as major causes of the low serum albumin. The high protein content of the pleural fluid supports the possibility of an increase in vascular permeability, rather than a primary increase in albumin degradation, as the cause of the decreased serum albumin. Secondary hypo-albuminaemia would then have contributed to the fluid retention by a reduction in plasma oncotic pressure.

Other mechanisms which have been proposed to contribute to the development of insulin oedema include thiamine deficiency with high output cardiac failure (Deckert, 1958; Shaper, 1966), excluded in our case, or an increase in glycogen-associated water stores (Leifer, 1928; Shaper, 1966). Glycogen stores in muscle and liver may vary by up to 500 g, each gram of glycogen being associated with 4 g of water (Olsson & Saltin, 1970), so this mechanism may contribute to the lesser degrees of weight gain associated with improved diabetic control but cannot explain the marked expansion of extracellular volume seen in patients with severe insulin oedema.

Regardless of the responsible mechanisms, the possibility of severe fluid retention should be borne in mind during the introduction of insulin therapy in severely malnourished diabetic patients.

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