

## Lower limbs edema by insulin glargine treatment: two other cases in pediatrics

Dario Iafusco<sup>1</sup> · Alessia Piscopo<sup>1</sup> · Santino Confetto<sup>1</sup> · Alessandra Cocca<sup>1</sup> · Giulia Pezzino<sup>2</sup> · Elisabetta Caredda<sup>1</sup> · Francesca Casaburo<sup>1</sup> · Pasquale Villano<sup>1</sup> · Loredana Russo<sup>1</sup> · Angela Zanfardino<sup>1</sup> · Francesco Prisco<sup>1</sup>

Received: 4 June 2015 / Accepted: 13 July 2015  
© Springer-Verlag Italia 2015

### Introduction

We have read with interest the recent paper of Succurro et al. [1] who described the case of bilateral lower limbs edema induced by insulin glargine (Lantus<sup>®</sup>). Here we report two cases of type 1 diabetic patients with lower limbs edema probably due to the glargine insulin administration.

### Case report 1

Marta, 13 years aged, suffered from type 1 diabetes from the age of 9 years.

She was admitted in our clinic for a progressive appearance of edema in both legs (Fig. 1). The edema was located in the pretibial and ankle region, bilaterally, mainly on the left; the skin was normal, not hot and not erythematous. Femoral and popliteal pulses were normal. Left and right ankle diameters were, respectively, 29.5 and 28 cm. The family history was negative for diseases associated with edema.

The metabolic control has always been good (yearly mean HbA1c 7.5 % 58 mmol/mol). She was on multi-daily injections (MDI) therapy, and the need of insulin was 0.7 U/kg/day.

Up to 3 months before the occurrence of edema, she had been treated with human insulin (Humulin R<sup>®</sup> and Humulin I<sup>®</sup>).

During the adolescence, as the lifestyle was changing, we decided to start basal bolus therapy. Boluses of fast analogues were administered on the arms and in abdomen, while insulin glargine was administered exclusively on both thighs, alternating the right and the left thigh every day.

All the most common causes of edema have been ruled out with specific investigations: Color Doppler ultrasound of the arteries and veins of the limbs excluded vascular diseases; ECG and transthoracic echocardiography excluded cardiac failure. Blood count, C-reactive protein (CRP) and VES, serum electrolytes, protein electrophoresis and the liver, thyroid and kidney function tests were within the normal range. Moreover, we rejected other causes of edema due to infection diseases. To exclude obstruction of the inferior vena cava or the thoracic duct, the patient underwent, respectively, abdominal ultrasound and chest X-rays, which did not show pathognomonic features. In addition, we also ruled out the Turner syndrome with the high-definition karyotype study.

Medical history, clinical examination and laboratory findings excluded the involvement of systemic diseases. No other medicaments except for insulin had been assumed so, suspecting that the cause of the edema could have been the local mechanism of absorption of basal insulin, we replaced insulin glargine with rapid and intermediate human insulin.

After 1-month edema was still present, but significantly reduced (diameter 25 cm in both legs).

The complete resolution occurred after 3 months from the suspension of glargine even if a slight worsening of metabolic control (HbA1c 8.5 % 69 mmol/mol) was observed.

---

Managed by Antonio Secchi.

---

✉ Dario Iafusco  
dario.iafusco@unina2.it

<sup>1</sup> Department of Pediatrics, Second University of Naples, Via S.Andrea delle Dame, 4, 80138 Naples, Italy

<sup>2</sup> Endocrinology, Department of Clinical and Molecular Bio-Medicine, Garibaldi-Nesima Hospital, University of Catania, Via Palermo 636, 95122 Catania, Italy



**Fig. 1** Bilateral edema of ankles and pretibial regions

### Case report 2

Agata, 17 years aged, with type 1 diabetes onset at the age of 8 years treated with human insulin. The patient had started basal bolus therapy at the dosage of 1.1 U/Kg/day with analogues Lispro (Humalog<sup>®</sup>) and Glargine (Lantus<sup>®</sup>), 1 month before the admission in our clinic for the onset of edema; the patient used to self-administer glargine always on the left leg where she developed unilateral progressive edema (Fig. 2).

The metabolic control was good (mean HbA1c 6.8 % 50 mmol/mol). We excluded all causes of edema and, according to our previous experience, we replaced glargine (Lantus<sup>®</sup>) with detemir (Levemir<sup>®</sup>) obtaining a complete remission after one month. This change in therapy did not compromise metabolic control (after 3 months the HbA1c was 7.4 % 57 mmol/mol).

### Discussion

Differently from the case report of Succurro et al. [1] about edema in an old type 2 diabetic patient, we observed edema, probably due to glargine, in two patients affected by type 1 diabetes mellitus.

We agree with the pathogenetic hypothesis of this phenomenon suggested by these authors: The delay in the



**Fig. 2** Edema of the left ankle

absorption of this kind of basal analogue, due to precipitates of insulin in the subcutaneous, may induce lipodystrophies and alterations of the tissue. In their description there was no evidence of swelling, while in our cases we evidenced both swelling and pitting. This difference could be due to the local fluid retentive action of insulin and/or to the structure of the subcutaneous of young people that is more elastic and thinner than in old people.

In our first case the remission of edema was obtained after the switching to human insulin, but in the second case the same result was achieved changing glargine with detemir.

The success of detemir therapy in our case was probably due to at least two reasons: The kinetic of this insulin that avoids the excessive accumulation in the subcutaneous tissue and the twice daily administration that probably promotes the faster absorption of insulin compared to the once daily schedule of glargine. However, in the literature several cases of generalized edema probably due to the treatment with insulin analogues (included detemir) have been described after the intensification of insulin treatment [2–4]. In our cases the metabolic control was optimal before and after the edema appearance and no further intensification of the therapy was applied.

In conclusion, despite the essential role of insulin in the management of patients with insulin deficiency, clinical use can result in adverse effects such, in rare cases, localized or generalized edema. In patients with edema on insulin therapy, after the exclusion of the most common causes of edema, the physician should take into account the causal role of insulin. If the patient is treated with glargine

it could be worthwhile to encourage the rotation of insulin injection sites or if necessary to switch this drug with other basal insulin.

**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical standard** The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Bioethics Committee at the Second University of Naples, Italy.

**Human and Animal Rights** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

**Informed consent** Informed consent was obtained from the parents of participants included in the study.

**References**

1. Succurro E, Ruffo M, De Sarro G, Gallelli L, Arturi F (2015) Bilateral lower limbs edema with “wooden” character induced by insulin glargine treatment. *Acta Diabetol* 52(4):809–811. doi:[10.1007/s00592-014-0707-7](https://doi.org/10.1007/s00592-014-0707-7)
2. Chelliah A, Burge MR (2004) Insulin edema in the twenty-first century: review of the existing literature. *J Investig Med* 52:104–108
3. Lee P, Kinsella J, Borkman M, Carter J (2007) Bilateral pleural effusions, ascites, and facial and peripheral oedema in a 19-year-old woman 2 weeks following commencement of insulin lispro and detemir—an unusual presentation of insulin oedema. *Diabet Med* 24:1282–1285
4. Adamo L, Thielke M (2013) Generalised insulin oedema after intensification of treatment with insulin analogues. *BMJ Case Rep*. doi:[10.1136/bcr-2012-007037](https://doi.org/10.1136/bcr-2012-007037)