

# Extreme enlargement of lower extremities mimicking elephantiasis in patients with severe insulin resistance syndrome; a novel phenotype

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## Objectives:

Severe insulin resistance syndromes are rare syndromes characterized by clinical features like:- acanthosis nigricans, ovarian hyperandrogenism in post pubertal females like hirsutism, oligomenorrhea and infertility. Major causes of severe insulin resistance are:-  
1) genetic defects in insulin receptor as in type A syndrome, 2) Antibodies to insulin receptor as in type B syndrome or antibodies to insulin itself, 3) congenital or acquired partial or generalized lipodystrophy.  
The goal of this report is to illustrate a unique clinical feature that has not been described in the literature in association with severe insulin resistance cause by receptor mutation (Type A Syndrome).

## Methods:

We report four females, at age (17, 18 and 21 yrs) who had been diagnosed as severe insulin resistance syndrome based on proved common insulin receptor mutation and the following clinical features:  
•Severe acanthosis nigricans  
•Hyperandrogenism (severe hirsutism and oligomenorrhea)  
•Pseudoacromegaly  
•Very high fasting insulin levels ranging from 500 to 1,700 pmol/L. (reference range 17.8-173) pmol/L  
In addition, all four patients were noted to have developed extreme lower extremities swelling of non-pitting nature before or after initiation of treatment. Pharmacological therapy including metformin, rosiglitazone or pioglitazone, spironolactone and oral contraceptive pills were used in therapy. Some symptoms improved partially but subjects continue to have remarkable and sometimes progressive lower limb swelling. In some instances, Glitazones were suspected to induce or increase the lower extremities swelling and were discontinued without improvement.  
All of the subjects except one underwent skin biopsy.

Patient #	Fasting Insulin	HbA1c	Testosterone	DHEA-S	IGF-1	BMI/ Wt at time of Dx BMI/Wt after 4 yrs
Patient # 1	847.5	5.7%	4.38	0.92	72	19/ 51 Kg 27 / 73 Kg
Patient # 2	570.9	4.8%	3.58	-	62	22/ 55 Kg 23/ 58 Kg
Patient # 3	1,774	-	3.23	8.2	-	24/ 61 Kg -
Patient # 4	197	4.1%	1.7	1.68	117	20/ 54 Kg -

### Reference:

- Fasting insulin reference range (17.8-173) pmol/L
- SHBG reference range (20-130) nmol/L
- Testosterone reference range (0.22-2.9) nmol/L
- DHEAS reference range (1.48-6.92) umol/L
- IGF-1 reference range (268-471) ng/mL

## Results:

- All patients above come from a tribe that is known to have family members with severe insulin resistance due to receptor mutation and clinical features of acanthosis nigricans.
- Extensive work up for the lower limb edema for of one of cases included: CT abdomen & pelvis, doppler for veins, lympho-angiogram all turned to be normal.
- Results of skin biopsy of lower leg showed normal subcutaneous tissue in one patient with perivascular lymphocytic infiltrate and occasional eosinophils in the other two patients. The significance of these biopsy findings is not clear.
- We suspect that the mechanism of the severe lower extremities swelling is also related to the stimulation of IGF1 receptors in the subcutaneous soft tissue by the excessive insulin level.

## Conclusions:

Awareness of this peculiar and rare clinical feature in patients with severe insulin resistance syndrome would help to avoid unnecessary work up for other causes of lower limb swelling.

The optimal management for this problem is not clear, and it seems to be more difficult to control than the other features associated with insulin resistance.

## References:

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