Generalized lipodystrophy (GL) is a rare, complex, and clinically heterogeneous disorder characterized by the widespread lack or loss of subcutaneous adipose tissue in most or all parts of the body, resulting in relative leptin deficiency.

Leptin

In normal physiology, leptin acts in the brain and periphery to regulate energy homeostasis and metabolic function in the body. In patients with GL, the widespread lack or loss of subcutaneous adipose tissue in most or all parts of the body, leads to relative leptin deficiency and associated metabolic abnormalities such as:

- Diabetes mellitus requiring high doses of insulin (requiring \( \geq 200 \text{ U/day} \))
- Hypertriglyceridemia: \( \geq 500 \text{ mg/dL} \)
- Insulin resistance
- Hyperphagia

Serum Leptin Levels

Endogenous leptin is low in patients with GL. However, current serum leptin testing may not be a reliable indicator of the degree of deficiency because:

- Leptin assays have not been standardized and can demonstrate variations between labs
- Assessment of a leptin assay results need to take into consideration gender, BMI, age, and metabolic abnormalities

There is no specific leptin level below which is diagnostic of GL:

- The diagnosis is based on clinical factors and metabolic abnormalities
- Medical experts agree that patients with GL have a relative leptin deficiency when compared to the general public
- Limited data exist regarding the range of leptin levels in patients with a confirmed diagnosis

Therefore, leptin level testing is an important tool to aid in the diagnosis of GL but is not sufficient, in and of itself.

Leptin Assay Performance Case Study

Three commercially available methods were compared:

- Linco RIA* (Linco Research, now Millipore)
- Diagnostic Systems Laboratories colorimetric ELISA
- Alpco RIA (Salem, NH)

When used to measure baseline leptin levels, there was a discrepancy between kits:

- Estimation of baseline leptin concentration in lean individuals were between 2.32 and 11.43 ng/ml, depending on kit
- Estimation of baseline leptin concentration in obese individuals were between 12.67 and 70.87 ng/ml, depending on kit

Baseline leptin concentration by kit

Subjects receiving 0.01 mg/kg r-metHuLeptin

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Linco (ng/ml)</th>
<th>DSL (ng/ml)</th>
<th>Alpco (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean Men (n=5)</td>
<td>2.32 ± 0.48</td>
<td>8.89 ± 1.96</td>
<td>11.43 ± 1.50</td>
</tr>
<tr>
<td>Obese Men (n=5)</td>
<td>12.67 ± 6.15</td>
<td>70.87 ± 27.31</td>
<td>18.09 ± 3.99</td>
</tr>
</tbody>
</table>

* Assay used in the NIH trials for generalized lipodystrophy
GL Diagnosis

The American Association of Clinical Endocrinologists (AACE) task force recommends considering a group of clinical characteristics that are supportive of GL. Identifying key clinical characteristics may lead to early detection of GL.

### Core clinical characteristic for GL

- Loss or absence of subcutaneous body fat in a generalized fashion

### Supportive clinical characteristics for GL

- Presence of diabetes with evidence of severe insulin resistance
  - Diabetes mellitus with requirement for high doses of insulin (eg, requiring ≥200 U/day, ≥2 U/kg/day, or currently taking U-500 insulin)
  - Ketosis-resistant diabetes
- Other evidence of severe insulin resistance
  - Acanthosis nigricans
  - PCOS or PCOS-like symptoms (hyperandrogenism, oligomenorrhea, and/or polycystic ovaries)
- Presence of hypertriglyceridemia
  - Severe hypertriglyceridemia (≥500 mg/dL)
  - Triglyceride levels that are nonresponsive to therapy and/or modifications to diet (≥250 mg/dL)
  - History of pancreatitis associated with hypertriglyceridemia
- Evidence of hepatic steatosis or steatohepatitis
  - Hepatomegaly and/or elevated transaminases in the absence of a known cause of liver disease (eg, viral hepatitis) may be consistent with nonalcoholic fatty liver disease
  - Radiographic evidence of hepatic steatosis (eg, on ultrasound or computed tomography)
- Family history of similar physical appearance and/or history of fat loss
- Prominent muscularity and phlebomegaly (enlarged veins) in the extremities
- Disproportionate hyperphagia (cannot stop eating, waking up to eat, fighting for food)
- Secondary hypogonadism in a male or primary/secondary amenorrhea in a female patient

Not all patients with the clinical characteristics listed in the table above will have GL.

Abbreviation: PCOS, polycystic ovary syndrome.

**References:**