Oral Glucagon-Like Peptide 1 Analog as an Adjuvant Therapy in Generalized Lipodystrophy

Yael Lebenthal,[1,2] Sharon Halperin,[3] Hagar Interator,[1,4] Avivit Brener,[1,2] and Rebecca J. Brown[1,5]

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Lipodystrophy syndromes are characterized by near-complete absence of subcutaneous adipose tissue (generalized lipodystrophy [GL]) or absence of adipose tissue in large body regions (partial lipodystrophy [PL]). Particularly in GL, hyperphagia from leptin deficiency, coupled with inability to store nutrients in adipocytes and consequent ectopic lipid in muscle and liver, leads to severe insulin resistance, dyslipidemia, and hepatic steatosis (1). Recombinant human methionyl leptin (metreleptin) mitigates metabolic complications of GL, but limits include daily injections and variable responses (2). Glucagon-like peptide 1 receptor agonists (GLP-1RA), widely prescribed for type 2 diabetes and obesity, have shown promise in addressing metabolic complications in PL, although data remain limited (3–5). We report the first successful use of an oral GLP-1RA in a patient with GL with inadequate diabetes control despite metreleptin and high-dose insulin, who transitioned off insulin after addition of an oral GLP-1RA, highlighting its potential as a novel therapeutic approach in this challenging scenario.

A 34-year-old female was diagnosed with acquired GL at age 8 years, presenting with characteristic body habitus and severe metabolic complications. Evaluation revealed generalized absence of subcutaneous fat, acanthosis, hepatosplenomegaly, triglycerides >6,000 mg/dL, and elevated transaminases.

She developed lipoatrophic diabetes (with positive GAD65 antibodies but preserved C-peptide) at age 10 years. Initially, glycemic control (HbA_{1c} ≤7% [53 mmol/mol]) was achieved with nutrition. However, with puberty, glycemia worsened; metformin was initiated, with later addition of rosiglitazone. These drugs briefly improved HbA_{1c}, but insulin became necessary by age 11 years. Over time, insulin requirements increased substantially, to 15 units/kg/day. At age 17 years, she started U-500, 600 units/day via pump.

When the patient was 17 years old, metreleptin was initiated with an institutional review board–approved protocol (clinical trial reg. no. NCT00025883, ClinicalTrials.gov).

Metreleptin initiation led to reduced insulin requirements, improved triglycerides, and resolution of hepatosteatosis and acanthosis. Her clinical course after age 17 years is summarized in Fig. 1*A*. At age 24 years, HbA_{1c} was 5.3% (34 mmol/mol); triglycerides were 109 mg/dL. Her metreleptin dose was reduced due to weight loss (BMI 16.3 kg/m^2); insulin dose was 1.4 units/kg/day.

Throughout follow-up, the family inquired about newer oral medications for type 2 diabetes, including GLP-1RA. In 2022, she initiated off-label oral semaglutide after discussion regarding potential side effects, lack of established efficacy, and need for close monitoring. Prior to semaglutide she used twice-daily glargine (260 units/day); HbA_{1c} was 7.7% (61 mmol/mol). Oral semaglutide was initiated at 3 mg daily and increased to 7 mg after 1 month, resulting in gradual reduction in insulin requirements. After 10 months insulin was discontinued; HbA_{1c} was 4.9% (30 mmol/mol). She experienced weight loss (BMI decrease from 18.9 to 14.6 kg/m^2), with no pancreatitis.

After initiating oral semaglutide she was able to travel without the burden of insulin. She emphasized the critical role of metreleptin in her management, calling it her "lifeline" and noting outstanding compliance. Since August 2023, she remains insulin free with exceptional glycemic control (HbA_{1c} <6% [42 mmol/mol] and percentage of time spent with glucose in target range 89%) (Fig. 1*B*).

GLP-1RA have emerged as promising therapies for PL. Retrospective analyses of injectable GLP-1RA in PL have demonstrated reduced weight and HbA_{1c}, suggesting potential for GLP-1RA to address key metabolic disturbances of lipodystrophy (3–5). Similar benefits of the injectable GLP-1RA, liraglutide, were observed in a mouse model of GL (6). Furthermore, glycemic benefit of the injectable GLP-1/glucose-dependent insulinotropic polypeptide receptor agonist (GIPRA) tirzepatide was recently reported in two patients with GL (7). Here, we demonstrate marked,

[1]*The Institute of Pediatric Endocrinology, Diabetes and Metabolism, "Dana-Dwek" Children's Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*
[2]*School of Medicine, Faculty of Medical & Health Sciences, Tel Aviv University, Tel Aviv, Israel*
[3]*Lipodystrophy United, Tel Aviv, Israel*
[4]*Nutrition & Dietetics Unit, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*
[5]*National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD*

Corresponding author: Rebecca J. Brown, brownrebecca@niddk.nih.gov

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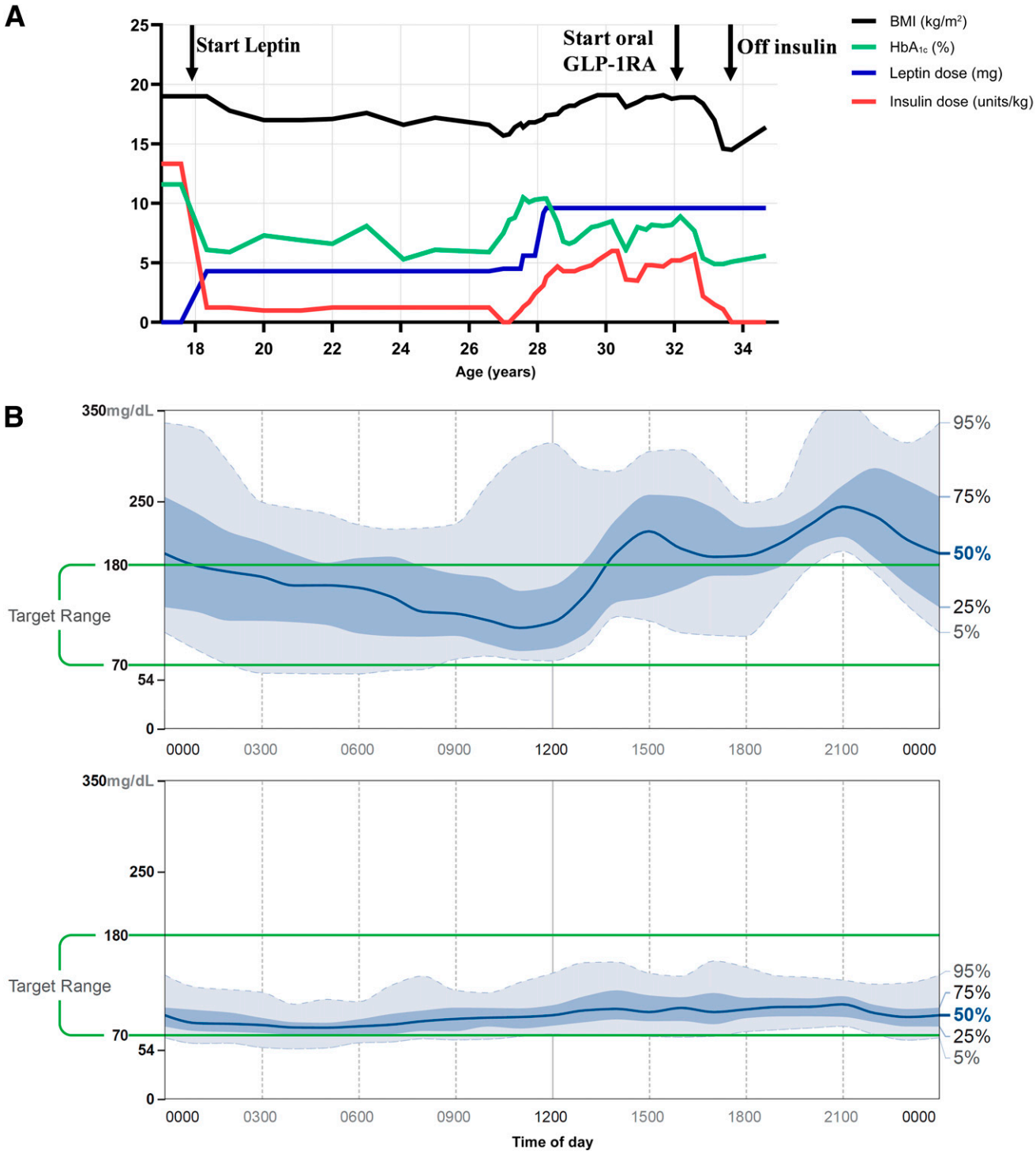

Figure 1—*A*: Timeline of BMI, HbA_{1c} levels, and insulin and metreleptin doses. *B*: Continuous glucose monitoring ambulatory glucose profile report before and 1 year after transition from insulin to oral semaglutide.

sustained improvement in insulin sensitivity and glycemia in a patient with GL treated with an oral GLP-1RA, semaglutide. Due to lack of subcutaneous tissue in GL, subcutaneous injections including insulin, metreleptin, and parenteral GLP-1RA or GLP-1/GIPRA are particularly painful and technically challenging. Thus, use of oral GLP-1RA, allowing discontinuation of high-dose insulin, is particularly impactful in improving quality of life.

While appetite-suppressing medications such GLP-1RA appear nonintuitive in patients with GL who do not have obesity, metreleptin likewise suppresses appetite, and reduced food intake underlies much of metreleptin's benefits (8). Furthermore, pathophysiology of insulin resistance in GL and obesity is quite similar, resulting from spillover of excess nutrients from adipose tissue with limited or no expansile capacity into ectopic tissues (9). Mechanisms by which GLP-1RA improve diabetes in lipodystrophy and obesity are similar, including

improved insulin sensitivity and secretion, reduced food intake and weight, and possibly central leptin sensitization (5).

Despite these promising findings, evidence for GLP-1RA in lipodystrophy remains limited. Lipodystrophies are heterogenous with variable severity; not all patients are suitable candidates for GLP-1RA. Pancreatitis has occurred and vigilant monitoring is required (3,5). Use of GLP-1RA in lipodystrophy should be approached cautiously, with understanding of potential risks and benefits.

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