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Adipose Tissue, Appetite, & Obesity

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Hormonal and Cardiometabolic Changes Associated with Diazoxide Choline Extended-Release (DCCR) Tablets in Patients with Prader-Willi Syndrome

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Background: Prader-Willi syndrome (PWS) is a rare genetic neurodevelopmental condition, characterized by hyperphagia, obesity, hormone deficiencies and behavioral/psychological manifestations. DCCR is under investigation as a treatment for hyperphagia in PWS through its actions on hypothalamic circuits involved in appetite regulation including NPY neurons and central inhibition of DMV neurons to improve insulin sensitivity. In addition to these effects, DCCR acts on pancreatic beta cells, to reduce glucose stimulated insulin secretion, which might have additional effects to reduce fat deposition in adipocytes, serum leptin concentrations and insulin resistance.

Objectives and methods: This analysis characterized changes in hormonal and cardiometabolic parameters in patients with PWS receiving oral daily DCCR. 125 participants with genetically-confirmed PWS ≥4 years old with hyperphagia were treated with DCCR in multi-center studies conducted at 29 sites in the US and the UK: a 13-week, Phase 3, double-blind, placebo-controlled study (DESTINY PWS) and its long-term, open-label extension study (analysis at 52 weeks). The target DCCR dose for these studies was ≥3.3 mg/kg with an optimal dose of 4.2 - 5.8 mg/kg. Overall, 103 patients received DCCR (100-525 mg/day) for 52 weeks. For all parameters, the baseline measurement was defined as (immediately prior to) start of DCCR treatment.

Results: Serum leptin, insulin, and HOMA-IR were significantly reduced following 52 weeks of DCCR administration. Results are expressed as Least square (LS) mean change from baseline [Standard Error (SE)]. There were significant decreases in: Leptin (ng/mL) = -11.08[1.26], $p<0.001$; Insulin (μIU/mL) = -2.5[0.69], $p<0.001$; and HOMA-IR = -0.5 [0.17], $p=0.003$. Serum adiponectin (μg/mL) was significantly increased: 1.82[0.41], $p < 0.001$. Fat mass measured by DXA was stable at 52 weeks.

Conclusions: The reductions in fasting leptin, insulin and HOMA-IR, and the increase in adiponectin with prolonged DCCR treatment in the absence of reductions in total body fat are consistent with improved insulin sensitivity that may also reflect improvement in leptin sensitivity and healthier body fat distribution, such as reduced visceral adiposity. This could result from both direct pancreatic and hypothalamus-to-periphery actions of DCCR. It remains to be determined if such beneficial metabolic changes also result in reduced systemic inflammation and cardiovascular health.

DCCR administration was associated with significant reductions in leptin, insulin, and HOMA-IR, increases in adiponectin and stabilization of body fat. These and other changes in cardiometabolic parameters suggest that DCCR may have long term health benefit in patients with PWS.

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