

Cycling GLP-1 receptor agonist treatment induces therapeutic resistance and increased adiposity

Authors and Affiliations

Anna J. Son^{1*}, Emmanuel Rapp^{1*}, Alex Wiezorek¹, Max G. Leung¹, Ronadip R. Banerjee^{2,#}, Thomas H. Leung^{1,3#}

1. Department of Dermatology, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America.
2. Division of Endocrinology, Department of Medicine, University of Arizona College of Medicine, Tucson, Arizona, United States of America.
3. Corporal Michael J. Crescenz Veterans Affairs Medical Center, Philadelphia, Pennsylvania, United States of America.

** These authors contributed equally as first authors.*

Correspondence:

Ronadip Banerjee

1656 E. Mabel St, MRB 430E, Tucson, AZ 85719

rrbanerjee@arizona.edu

Thomas Leung

421 Curie Blvd, BRB 1006, Philadelphia PA 19104

thl@pennmedicine.upenn.edu

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GLP-1 receptor agonists (GLP-1 RA) have revolutionized obesity management, yet “real-world” use is characterized by frequent treatment discontinuation and re-initiation (1, 2). More than half of patients discontinue therapy within 24 months, and many subsequently restart (1). Because weight regain is rapid following cessation, and up to 40% of GLP-1-RA-induced weight loss reflects lean mass, repeated cycling may exert a cumulative metabolic toll given the limited capacity for skeletal muscle recovery (3-5). Here, we define the metabolic impact of GLP-1 RA cycling *in vivo*.

We modeled intermittent GLP-1 RA therapy in diet-induced obese male C57BL/6J mice. Mice assigned to continuous treatment received daily semaglutide for 4 months. In contrast, the cycled group underwent two rounds of 2-week semaglutide exposure followed by 2-week withdrawal before transitioning to continuous treatment (Figure 1A, Supplemental Methods).

During the initial treatment phase (cycle 1), weight loss was comparable between groups. Upon semaglutide withdrawal, cycled mice rapidly regained weight. Re-initiation of semaglutide (cycle 2) induced weight loss; however, cycled mice failed to reach the prior weight nadir achieved during cycle 1 (Figure 1B). After a second withdrawal period, body weight in cycled mice rebounded to 7% above baseline. A third course of semaglutide (cycle 3) also produced a markedly attenuated weight loss response, and cycled mice weighed 20% more than continuously treated controls (Figure 1B-C; Supplementary Figure 1A-B). Notably, this “therapeutic resistance” persisted despite 62 days of uninterrupted semaglutide treatment (Days 58-120).

Body composition analysis by EchoMRI (Day 83) demonstrated increased total and percent fat mass and reduced percent lean mass in cycled mice versus continuously treated controls, while absolute lean mass was unchanged (Figure 1D, Supplementary Figure 1C). At study end (day 120), cycled mice exhibited expansion of eWAT, iWAT, and BAT depots, accompanied on histology by adipocyte hypertrophy (Figure 1E-1F, Supplementary Figure 1D-1E). Skeletal muscle weights were comparable between groups (Supplementary Figure 1F). Together, these findings indicate that intermittent semaglutide exposure preferentially promotes adipose accrual despite preservation of absolute lean mass.

Metabolic phenotyping revealed increased serum leptin and impaired glucose tolerance in cycled mice (Figure 1G, Supplementary Figure 1G). In contrast, insulin tolerance testing revealed no difference between groups, suggesting that the observed glucose intolerance is not driven by peripheral insulin resistance (Supplementary Figure 1H). Indirect calorimetry revealed no differences in oxygen consumption (VO_2), carbon dioxide production (VCO_2), energy expenditure, food or water intake, or locomotor activity between groups. However, respiratory exchange ratio (RER) was

reduced in cycled mice, consistent with a shift toward increased lipid utilization (Supplementary Figure 2). Increased lipid utilization in the absence of weight reduction suggests a compensatory metabolic adaptation rather than enhanced energy expenditure. Because differences in body composition are intrinsic to the cycling phenotype, these studies assess the integrated metabolic consequences of treatment interruption but do not distinguish primary effects on energy balance from secondary effects of altered lean and fat mass.

A second independent cohort reproduced these findings (Figure 1H-1I, Supplementary Figure 3). Following semaglutide withdrawal (cycle 2), cycled mice again exhibited rapid weight regain, reaching 9% above baseline. Re-initiation of treatment (cycle 3) resulted in attenuated weight loss, with cycled mice remaining 20-25% heavier than continuously treated controls (Figure 1J).

Taken together, these data demonstrate that intermittent GLP-1 RA exposure rapidly attenuates therapeutic efficacy, with loss of response evident by the second cycle and resulting in ~20% higher body weight after three exposures compared to continuous treatment. We propose that repeated treatment interruptions lead to a cumulative deficit in lean mass that is not fully recovered during off-treatment intervals. Consequently, each successive cycle begins from a progressively altered body composition characterized by increased adiposity relative to lean mass. Under these conditions, homeostatic mechanisms may preferentially defend remaining lean mass, establishing a physiological constraint that limits further weight loss despite continued GLP-1 RA exposure. Future studies are needed to define these molecular mechanisms. Jiang and colleagues recently reported similar attenuation of weight loss using liraglutide in aged UM-HET3 mice (6). Despite differences in mouse strain, age, and GLP-1 RA used, the concordance between studies suggests that this attenuation of efficacy may represent a class effect rather than a drug-specific phenomenon. As both studies were performed in obese male mice, validation in females and in human populations will be essential to determine translational relevance. These findings raise concern that cycling GLP-1 RA may promote therapeutic resistance and unfavorable metabolic outcomes, with important implications for long-term clinical management and treatment durability.

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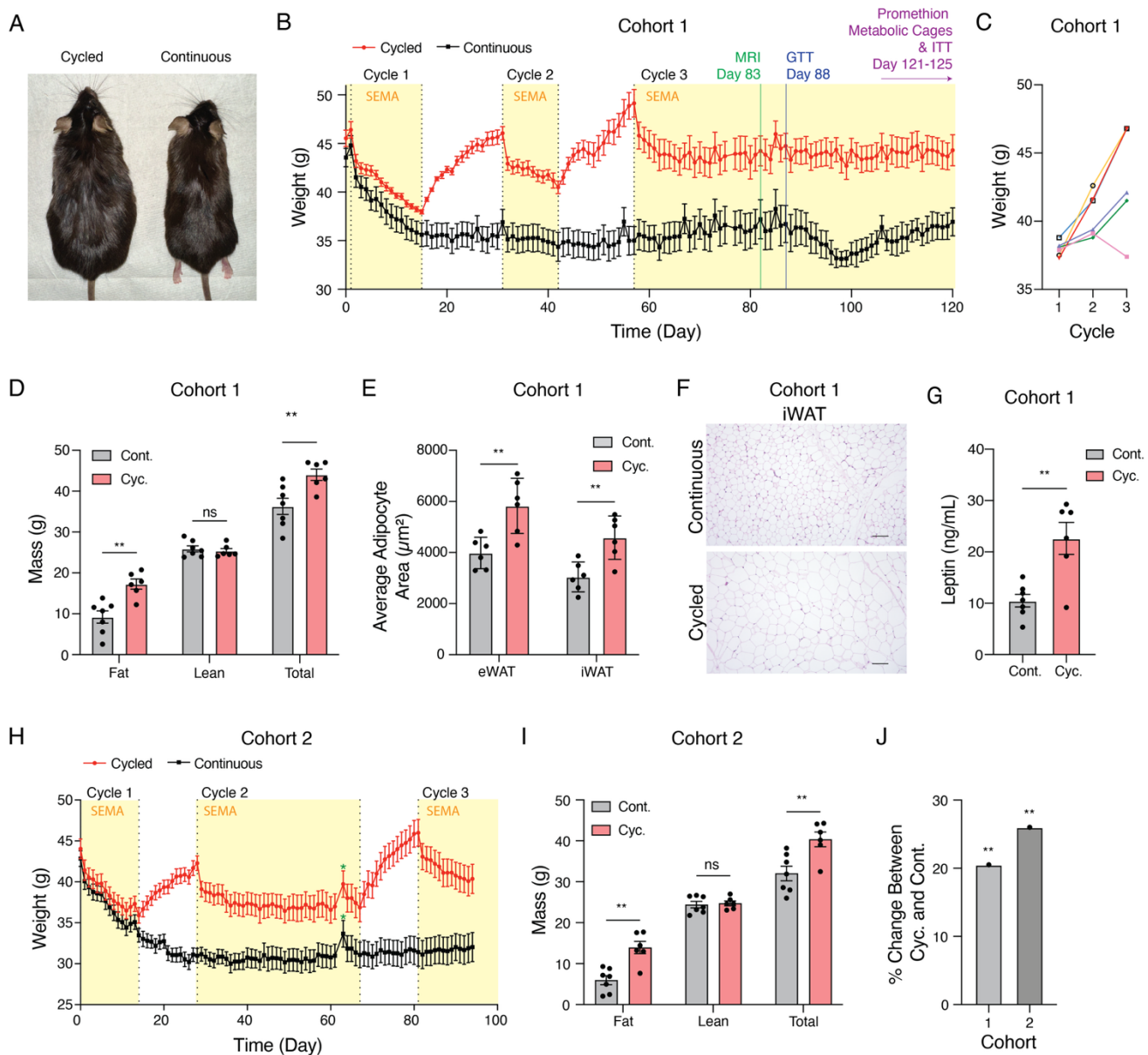


Figure 1. Cycling GLP-1 receptor agonist treatment induces therapeutic resistance and rebound obesity

(A) Representative image of cycled and continuous semaglutide (SEMA)-treated mice on day 120. (B) Body weight trajectories of Cohort 1 cycled (red, n = 6) and continuous (black, n = 7) mice. (C) Body weights of individual cycled mice 14 days after each cycle. (D) Fat, lean, and total mass by EchoMRI on day 83. (E) Mean adipocyte area in eWAT and iWAT, quantified from representative H&E-stained sections in (F) (scale bar, 100 μm). (G) Plasma leptin levels in Cohort 1. (H) Body weight trajectories of Cohort 2 cycled (red, n = 6) and continuous (black, n = 7) mice over 95 days; green star, one missed treatment day. (I) Fat, lean, and total mass by EchoMRI on day 95. (J) Percent weight change in cycled versus continuous mice across both cohorts. Unpaired two-tailed Student's t test. ns, not significant; *P < 0.05, **P < 0.01. Mean \pm SEM.