

RESEARCH LETTER **OPEN ACCESS**

Prevention of Weight Regain After GLP1RA Cessation With Oral TIX100

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1 | Background

Weight loss has become a medically attainable goal with glucagon-like peptide 1 receptor agonists (GLP1RAs) [1–3], but weight maintenance after GLP1RA-mediated weight loss and GLP1RA discontinuation has remained elusive. Approximately 50% of GLP1RA users discontinue treatment within 1 year, and ~70% within two years [4, 5]. Multiple reasons contribute to this discontinuation of GLP1RAs, including gastrointestinal side effects, loss of lean/muscle mass, need for injections and high cost [6–8]. In addition, a striking weight rebound has been reported in individuals after GLP1RA discontinuation irrespective of treatment duration [9]. Thus, non-GLP-based oral therapies that are well tolerated and do not lead to loss of lean mass yet maintain the weight loss attained with GLP1RAs are urgently needed.

TIX100 was originally developed as an oral anti-diabetic and specific inhibitor of thioredoxin-interacting protein (TXNIP) [10], a detrimental protein involved in diabetic beta cell loss and islet cell dysfunction. TIX100 has been approved as an investigational new drug by the U.S. Food and Drug Administration (FDA IND 166113) [11] based on extensive safety assessments including clinical chemistry, organ weights and pathology, and histology of relevant tissues after 4-week TIX100 treatment in rodents and dogs and has already been found to be safe and well tolerated in a Phase 1 human trial. Interestingly, we recently discovered that TIX100 also has beneficial effects on weight control in mice [12]. In particular, 12 weeks of oral TIX100 led to a mild, but significant inhibition of weight gain in the context

of high-fat diet (HFD)-induced obesity, which was mediated by reduced food intake rather than increased energy expenditure [12]. This raised the intriguing question as to whether TIX100 might help prevent weight regain after GLP1RA discontinuation. The current preclinical studies were therefore aimed at determining the effects of oral TIX100 on post-GLP1RA weight rebound.

2 | Methods

2.1 | Animal Studies

All mouse studies were approved by the University of Alabama at Birmingham Animal Care and Use Committee. Wild-type, 8-week-old male C57Bl/6J mice (RRID:IMSR_JAX:000664) were rendered obese by ad libitum access to a high-fat, high-sucrose diet (HFD; #D12331 Research Diets, New Brunswick, NJ).

2.2 | GLP1RA And TIX100 Treatment

The GLP1RA, semaglutide was purchased from AdipoGen (#AG-CP3-0040-M005, AdipoGen Life Sciences Co., San Diego, CA). The substituted quinazoline-sulfonamide TXNIP inhibitor, TIX100 was a generous gift from TIXiMED Inc. Mice on HFD were treated for 2 weeks with semaglutide (10 nmol/kg subcutaneously every other day), followed by 4-week treatment with oral TIX100 (40 mg/kg/day in the drinking water) or vehicle (water only) as described previously [10, 12]. Please see

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Supporting Information: Supplementary Appendix for additional methods information.

2.3 | Quantitative Magnetic Resonance

Body composition, including fat mass and lean mass, was measured at the end of the study using quantitative magnetic resonance (QMR) (EchoMRI, Echo Medical Systems) at the UAB Diabetes Animal Physiology Core, which remained blinded to the experimental group of the animals.

2.4 | Appetite-Regulating Hormones

Serum leptin was assessed by ELISA (Crystal Chem #90030, Itasca, IL) [12].

2.5 | Statistical Analysis

Was performed by an independent and blinded statistician. Outcomes were summarised using the mean and standard deviation (SD) at each time point. Before initiation of TIX100 treatment, changes in body weight over time (0, 8 and 10 weeks) were evaluated using a linear mixed-effects model (LMM) with a random intercept. Post hoc comparisons between adjacent time points were performed using paired *t*-tests with Bonferroni correction. To assess the effect of TIX100, body weight at Week 14 was compared between groups using analysis of covariance (ANCOVA), adjusting for body weight at Week 10. Within-group changes were evaluated using paired *t*-tests with Bonferroni correction. Lean mass, fat mass, food intake and leptin at Week 14 were compared between groups using two-sample *t*-tests. Effect sizes were calculated using Cohen's *d*, which quantifies the standardised mean difference between time points or groups. Assumptions of normality and homogeneity of variance

were assessed using the Shapiro–Wilk test and Levene's test, respectively.

3 | Results and Conclusions

After 8 weeks on the HFD, mice had gained over 50% of their body weight resulting in marked obesity (Figure 1A). Treatment with semaglutide led to a consistent and highly significant weight loss over the following 2 weeks while the mice continued on the HFD (Figure 1A). However, within 4 weeks of semaglutide discontinuation, water-only/vehicle-treated mice regained their weight (Figure 1B), mimicking the weight rebound observed in patients stopping GLP1RA after weight loss. In contrast, TIX100-treated mice maintained their weight over the 4 weeks despite continued HFD exposure (Figure 1C). In fact, comparison of the associated weight changes demonstrated the significant difference between TIX100-treated and vehicle-treated mice, with a mean 7.7 g weight rebound occurring only in vehicle-treated animals (Figure 2A). Importantly, this observed weight difference was not due to any loss of lean mass in the TIX100-treated mice (Figure 2B) but rather associated with a reduction in fat mass (Figure 2C) and food intake (Figure 2D), as well as a decrease in serum leptin (Figure 2E). These findings are consistent with recent observations during long-term TIX100 treatment without prior GLP1RA-induced weight loss that lowered HFD-induced weight gain while not affecting lean mass [12]. These previous studies also had demonstrated that TIX100 improved glucose control, hyperglucagonemia and hyperinsulinemia and did not cause any increase in energy expenditure, activity or appetite-regulating hormones, but instead promoted leptin sensitivity and resulted in decreased food intake [10, 12]. The current findings suggest that the same mechanisms are involved in the protective effects against post-GLP1RA weight regain observed in the present study. While dual- and triple-agonists of GLP1, glucose-dependent insulinotropic peptide and glucagon receptors, may

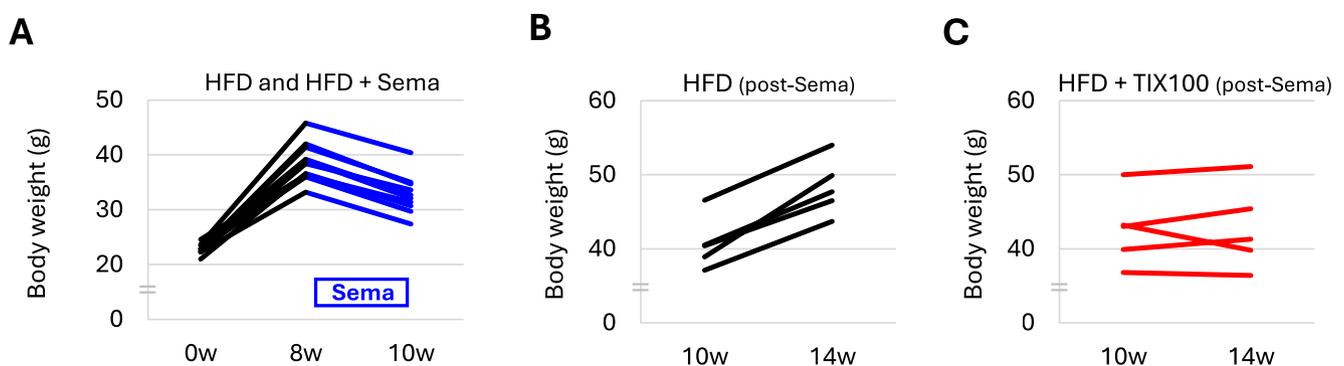


FIGURE 1 | Individual body weights of mice in response to HFD, semaglutide or TIX100. (A) Body weights of 8-week-old, male C57BL/6J mice during 8 weeks of HFD-induced weight gain and 2 weeks of GLP1RA-induced weight loss with subcutaneous semaglutide (Sema) treatment. Linear mixed effects model (LMM) analysis indicated a significant change in body weight over time ($F_{2,18}=227.7, p<0.0001$). After 8 weeks on the HFD, mean body weight increased from (mean \pm SD) 31.1 ± 3.1 to 48.0 ± 3.9 g, representing a mean gain of 16.9 g (95% CI: 14.8–18.9; Cohen's $d=13.1$; $t_9=21.1, p<0.0001$). Following 2 weeks of semaglutide treatment, mice experienced a significant weight reduction of 6.4 g (95% CI: 4.3–8.4; Cohen's $d=2.2$; $t_9=7.96, p<0.0001$), resulting in a mean weight of 41.6 ± 4.2 g at Week 10. After discontinuation of semaglutide, mice receiving vehicle, (HFD post-Sema), regained body weight, increasing from a mean weight of 40.7 ± 3.6 g at Week 10 to 48.4 ± 3.9 g at Week 14, ($t_4=8.9, p=0.0009$) (B). In contrast, mice treated with TIX100 (HFD + TIX100 post-Sema) maintained stable body weight, measuring 42.6 ± 4.9 g at Week 10 and 42.8 ± 5.7 g at Week 14 ($t_4=0.22, p=0.8383$) (C). Lines represent trends of individual mouse body weights, $n=5-10$ mice, (A) LMM, (B, C) Paired *t*-tests with Bonferroni correction.

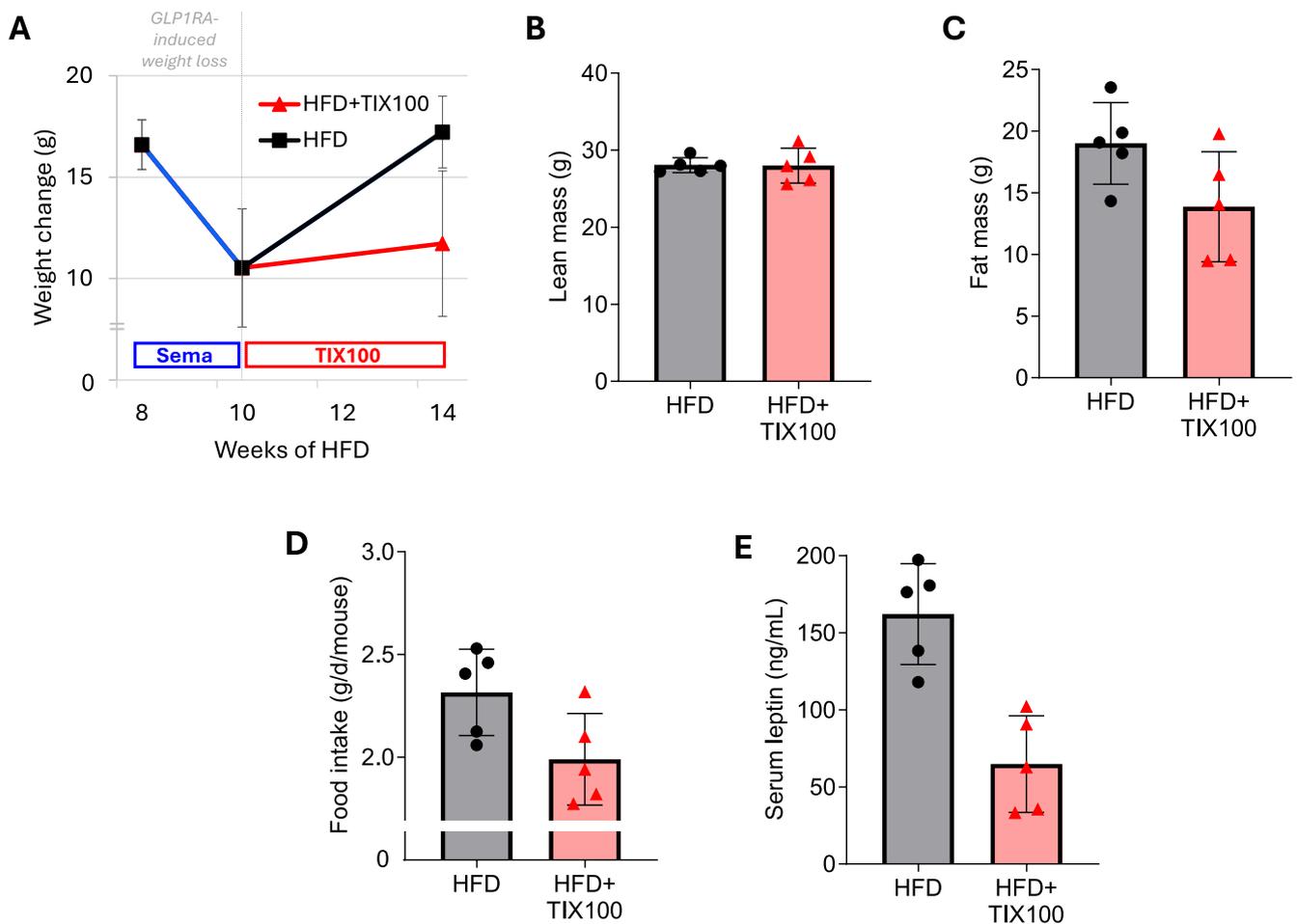


FIGURE 2 | Effects of TIX100 on post-GLP1RA weight change and body composition. (A) Comparison of weight changes after discontinuation of semaglutide with and without TIX100 treatment. After discontinuation of semaglutide, mice receiving vehicle while continuing on the HFD (HFD) had a mean gain in body weight of 7.7 g (95% CI: 5.3–10.1; Cohen's $d = 4.0$; $t_4 = 8.9$, $p = 0.0009$), whereas mice treated with TIX100 (HFD + TIX100) had no significant increase in body weight. After adjusting for body weight at Week 10, body weight at Week 14 was significantly lower in the TIX100-treated mice compared with vehicle-treated mice, with a mean difference of 7.5 g (95% CI: 4.0–10.9; Cohen's $d = 1.1$; $F_{1,7} = 26.2$, $p = 0.0014$). Lean mass as assessed by quantitative magnetic resonance at Week 14 was not significantly different between vehicle group (28.1 ± 1.0 g) and TIX100 group (28.0 ± 2.3 g; $t_8 = 0.06$, $p = 0.9553$) (B). In contrast, fat mass was 5.1 g (95% CI: 2.7–7.5; Cohen's $d = 1.3$; $t_8 = 2.1$, $p = 0.0725$) lower in TIX100-treated mice (13.9 ± 4.5 g) compared to vehicle-treated mice (19.0 ± 3.3 g) (C). Average food intake during 4 weeks after semaglutide discontinuation was significantly reduced in the TIX100 group (2.0 ± 0.2), with a mean difference of 0.33 (95% CI: 0.15–0.41; Cohen's $d = 1.5$; $t_8 = 2.4$, $p = 0.0444$), compared to the vehicle group (2.3 ± 0.2) (D). Serum leptin levels as assessed by ELISA were significantly reduced in the TIX100 group (64.8 ± 31.3 ng/mL) as compared to the vehicle group (162.1 ± 32.8 ng/mL), with a mean difference of 97.3 ng/mL (95% CI: 50.5–144.1; Cohen's $d = 3.0$; $t_8 = 2.4$, $p = 0.0014$) (E). Means \pm SD, $n = 5$ –10 mice, (A) ANCOVA; (B–E) Two-sample t -tests.

provide more effective weight loss and less severe side effects, discontinuation seems to invariably lead to weight rebound. Also, with GLP1RAs, 15%–40% of the weight loss is often due to loss of lean/muscle mass [13] and despite significant efforts, this issue has remained unresolved. Moreover, even though the recent FDA approval of oral semaglutide now offers patients an oral administration option, the side effects remain the same. Thus, establishing a well-tolerated, oral approach to prevent weight regain after medically induced weight loss remains an important unmet need and based on the current results, TIX100 may represent a promising candidate in this regard. Also, since oral TIX100 does not promote GLP1R action, it is theoretically not associated with GLP1RA-related gastrointestinal side effects and has been well tolerated in initial human safety studies for other indications. The main limitations of the current study

include its use of only male mice, shorter duration and preclinical nature and thus sex-comparative studies, mechanistic studies and extended follow-up are still required and the beneficial effects of TIX100 on weight maintenance after GLP1RA cessation will need to be validated in larger studies and, most importantly, in human trials.

Author Contributions

S.J. performed and analysed the experiments. J.C. and G.J. helped with all the mouse studies. G.X. performed the leptin assays. P.L. conducted all the statistical analyses. A.S. conceived the project, wrote the manuscript and is the guarantor of this work. As such she had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflicts of Interest

A.S. also serves as the co-founder and CSO/CMO of TIXiMED Inc. Bias was mitigated using prespecified endpoints, independent statistical analyses, and an institutional conflicts of interest management plan.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** dom70633-sup-0001-Supinfo.docx.