COMMENTARY

Targeting Adipose Inflammation and Energy Expenditure to Sustain Metabolic Health After Weight Loss

Siegfried Ussar

Diabetes 2025;74:1464–1465 | https://doi.org/10.2337/dbi25-0027

Obesity is an enormous global health problem and a main cause for the rapidly increasing numbers of patients suffering from type 2 diabetes (1). Until recently, pharmacological interventions to treat obesity were thought to reach body weight losses of up to 10%. With the groundbreaking introduction of glucagon-like peptide 1 (GLP-1)-based monoreceptor and polyreceptor agonists, weight loss exceeding 20% can now be reached, providing the first nonsurgical interventions to have profound effects on body weight as well as glucose and lipid homeostasis (2). These results are truly game changing, and the next generation of weight loss drugs aims to lower side effects and further increase body weight loss (3). However, as with the traditional interventions of diet and exercise, the effects of weight loss drugs diminish when they are discontinued, resulting in weight regain (4). Although long-term studies are still lacking, various reasons for discontinuation of these drugs, such as costs and side effects potentially in combination with frustration of reaching a weight loss plateau, could result in large numbers of individuals being exposed to significant weight regain.

This is especially problematic because weight regain could accelerate the development of insulin resistance and progression toward type 2 diabetes compared with weight gain without prior weight loss (5–7). While the regulation of body weight is now well established to be primarily regulated by the central nervous system, the development of systemic insulin resistance often initiates with an increase in dysfunctional white adipocytes (8). In line with these data, a number of studies over the last decade have shown that adipose tissue retains a memory of past obesity in the form of increased adipose tissue inflammation (5,6,9). Recently, Hinte et al. (7) showed that white adipose tissue retains an epigenetic memory of past obesity, resulting in increased adipose tissue inflammation and fibrosis. Thus, restoration of adipose tissue function upon weight loss is an essential future drug target to follow or accompany weight loss drugs.

In the current issue of *Diabetes*, Léon et al. (10) address exactly this issue by studying the effects of a previously published (11) GLP-1/dexamethasone (GLP-1/Dexa) conjugate on body weight, systemic glucose metabolism, and adipose tissue function following weight loss in diet-induced obese mice. The authors find that GLP-1/Dexa has superior effects on body weight loss and glucose homeostasis compared with GLP-1 or dexamethasone individually. However, it is surprising that the authors find a body weight setpoint in their mouse model, as the lack thereof has been an issue in preclinical studies aiming to target the human body weight setpoint. In contrast to other studies, Léon et al. exposed young (4-week-old) mice to an obesogenic high-fat diet, which might be responsible for this phenomenon and should be investigated in greater depth in the future.

Mechanistically, Léon et al. show that GLP-1/Dexa increases thermogenic gene expression in brown adipose tissue (BAT) and likely activity (Fig. 1). No metabolic cage data are provided that would allow further conclusions on systemic energy metabolism and a potentially increased energy expenditure due to increased BAT activity in these mice. However, these experiments would most likely require very large numbers of animals to detect small differences in energy expenditure or experiments conducted for an extended period. Importantly, the effects of BAT on the observed weight loss phenotype somewhat complicate extrapolation of these research findings to humans who mostly lack highly active BAT. Hence, it will be very informative to perform similar studies in mice housed at thermoneutrality to exclude, as much as possible, the metabolic effects of BAT and beige adipose tissue in this preclinical model (12).

More importantly, the authors find that GLP-1/Dexa reduces adipose tissue inflammation and improves systemic

Research Unit Adipocytes and Metabolism, Helmholtz Diabetes Center, Helmholtz Zentrum München, German Research Center for Environmental Health GmbH, Neuherberg, Germany
German Center for Diabetes Research, Neuherberg, Germany

Corresponding author: Siegfried Ussar, siegfried.ussar@helmholtz-munich.de

© 2025 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at https://www.diabetesjournals.org/journals/pages/license.

See accompanying article, p. 1525.

Downloaded from http://diabetesjournals.org/diabetes/article-pdf/74/9/1464/839583/dbi250027.pdf by HELMHOLTZ ZENTRUM MUENCHEN user on 17 October 2025

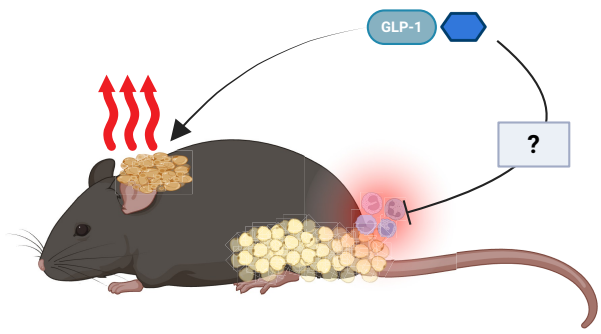

Figure 1—GLP-1/Dexa has additional effects on body weight loss by increasing BAT thermogenesis. In parallel, GLP-1/Dexa lowers white adipose inflammation through reducing activity of the CCR2/CCL2 axis via a currently unidentified cell population within or outside adipose tissue. Image created with BioRender.com.

glucose metabolism, which can be phenocopied by inhibition of the CCR2/CCL2 inflammatory pathway through depletion of peripheral blood Ly6C^{hi} monocytes using an anti-CCR2 antibody treatment. However, how GLP-1/Dexa facilitates and potentially interacts with CCR2 action remains unclear (Fig. 1). The identification of Ly6C^{hi} monocytes as the primary facilitators of the GLP-1/Dexa effects on adipose tissue inflammation is interesting, but it raises the question of whether the corresponding human CD14^{+}/CD16^{-} classical monocytes would facilitate the same effect. Moreover, single-cell RNA sequencing data from the adiposetissue.org database (13) do not indicate expression of the GLP1R in adipose tissue monocytes or macrophages, further suggesting, as indicated by the authors, an indirect effect of the drug. Thus, some interesting and potentially important insights are still missing concerning GLP-1/Dexa action on adipose tissue upon weight loss.

However, the article by Léon et al. addresses two important points for metabolic management following weight loss. First, increasing energy expenditure, in addition to reducing food intake, should provide important assistance in weight management, usually affected by reduced energy expenditure in obesity (14). The contribution of human BAT to this, however, remains unclear (15). Conversely, increasing white adipose tissue or skeletal muscle energy expenditure would be a tempting approach, with the latter ideally combined with an increase in muscle mass to counteract weight loss–induced sarcopenia. Second, elimination or reduction of adipose tissue inflammation has profound positive effects on glucose and potentially also lipid homeostasis. To this end, the current study certainly makes a strong case for added benefits of GLP-1/Dexa compared with GLP-1 alone or other GLP-1–based polyagonists. Identification of the target cells will certainly boost interest in the clinical development of this drug. However, given the superior weight loss effects of GLP-1/gastrointestinal polypeptide dual agonist or other polyagonists, GLP-1/Dexa might be primarily used following weight loss or in combination with other more potent weight loss drugs. Thus, it will be interesting to see if GLP-1/Dexa can also ameliorate the weight regain–associated deterioration of glucose metabolism following GLP-1 or GLP-1–based coagonist–induced weight loss. Finally, recent data suggest that epigenetic changes in adipocytes are a main mechanism of obesogenic memory (7). Thus, ideal pharmacological interventions would target these epigenetic alterations. However, if applied systemically, this approach could raise major safety concerns. Hence, the identification of adipocyte selective drug delivery vehicles could provide essential novel and safe strategies to restore adipose tissue function and health following weight loss (16).

Funding. S.U. receives project funding from the German Center for Diabetes Research (DZD).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

1. Rubino F, Cummings DE, Eckel RH, et al. Definition and diagnostic criteria of clinical obesity. Lancet Diabetes Endocrinol 2025;13:221–262
2. Kusminski CM, Perez-Tilve D, Müller TD, DiMarchi RD, Tschöp MH, Scherer PE. Transforming obesity: the advancement of multi-receptor drugs. Cell 2024;187:3829–3853
3. Grandl G, Novikoff A, Liu X, Müller TD. Recent achievements and future directions of anti-obesity medications. Lancet Reg Health Eur 2024;47:101100
4. Wilding JPH, Batterham RL, Davies M, et al.; STEP 1 Study Group. Weight regain and cardiometabolic effects after withdrawal of semaglutide: the STEP 1 trial extension. Diabetes Obes Metab 2022;24:1553–1564
5. Bernecker M, Lin A, Feuchtinger A, Molenaar A, Schriever SC, Pfluger PT. Weight cycling exacerbates glucose intolerance and hepatic triglyceride storage in mice with a history of chronic high fat diet exposure. J Transl Med 2025;23:7
6. Schmitz J, Evers N, Awazawa M, et al. Obesogenic memory can confer long-term increases in adipose tissue but not liver inflammation and insulin resistance after weight loss. Mol Metab 2016;5:328–339
7. Hinte LC, Castellano-Castillo D, Ghosh A, et al. Adipose tissue retains an epigenetic memory of obesity after weight loss. Nature 2024;636:457–465
8. Bluher M. Understanding adipose tissue dysfunction. J Obes Metab Syndr 2024;33:275–288
9. Fischer IP, Irmler M, Meyer CW, et al. A history of obesity leaves an inflammatory fingerprint in liver and adipose tissue. Int J Obes (Lond) 2018; 42:507–517
10. Léon S, Benoit J, Clark S, et al. GLP-1–mediated targeting of inflammation corrects obesogenic memory in male mice. Diabetes 2025;74:1525–1534
11. Quarta C, Clemmensen C, Zhu Z, et al. Molecular integration of incretin and glucocorticoid action reverses immunometabolic dysfunction and obesity. Cell Metab 2017;26:620–632.e6
12. Fischer AW, Cannon B, Nedergaard J. Optimal housing temperatures for mice to mimic the thermal environment of humans: an experimental study. Mol Metab 2018;7:161–170
13. Zhong J, Zareifi D, Weinbrenner S, et al. adiposetissue.org: a knowledge portal integrating clinical and experimental data from human adipose tissue. Cell Metab 2025;37:566–569
14. Careau V, Halsey LG, Pontzer H, et al.; IAEA DLW database group. Energy compensation and adiposity in humans. Curr Biol 2021;31:4659–4666.e2
15. Cypess AM, Cannon B, Nedergaard J, et al. Emerging debates and resolutions in brown adipose tissue research. Cell Metab 2025;37:12–33
16. Onogi Y, Khalil AEMM, Ussar S. Identification and characterization of adipose surface epitopes. Biochem J 2020;477:2509–2541

Downloaded from http://diabetesjournals.org/diabetes/article-pdf/74/9/1464/839583/db250027.pdf by HELMHOLTZ ZENTRUM MUENCHEN user on 17 October 2025