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EDITORIAL COMMENT

Cardiometabolic Diseases

Still in Search of the Optimal Mouse Model*

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The interplay between metabolic disorders and nonischemic cardiac dysfunction constitutes the subject of extensive research efforts over the past 50 years. Metabolism is all about the flow of nutrients, which serve as fuels that are catabolized for production of cellular energy, as well as substrates for anabolic processes that mediate synthesis of biological macromolecules and maintain cellular homeostasis. The body has mechanisms to handle excess intake of nutrients, usually by storing them in various organs either for a short or for a longer period. Although fuels are stored in ways that mostly make them chemically neutral, excessive accumulation is associated with health comorbidities. Significant improvements in analytical chemistry methods in the past 25 years, along with the development of high-throughput transcriptomic and proteomic analyses, have allowed the research community to start deciphering the metabolic biology pathways with comprehensive experimental approaches that assess gene expression, proteome, and metabolome changes. These technological advancements have taken place along with efforts to optimize experimental animal models for studying cardiometabolic diseases. For this purpose, both genetic and nutritional mouse models have been used, which bear their own strengths and weaknesses. Those models mimic certain components of metabolic diseases or combination of them, such as hyperphagia, obesity, hyperlipidemia, hyperglycemia, hypertension, and others, aiming to recapitulate human pathophysiology and explore the therapeutic potential of applied interventions.

In this issue of *JACC: Basic to Translational Science*, Maurya et al[1] present a very interesting study in which they used nuclear magnetic resonance technology, that this group has pioneered in the field of cardiac metabolism, to assess differences among animal models of cardiometabolic disease. The investigators compared cardiac lipid dynamics in a genetic model of hyperphagia-induced type 2 diabetes, in chow-fed mice that are deficient for leptin receptor (*db*/*db*) and in C57BL/6 mice that were fed on a Western diet (WD) for either 20 or 24 weeks. The WD contained 42% carbohydrate (35% caloric equivalence), with one-half being sucrose and 22% fat (45% caloric equivalence), consisting of saturated, monounsaturated, and polyunsaturated fat. The investigators found that WD-induced diabetes incurs distinct changes in cardiac triglyceride dynamics compared with the hyperphagia model (**Figure 1**). Specifically, they show that although both mouse models have higher triglyceride content compared with chow-fed wild-type mice, triglyceride turnover is increased in *db*/*db* mice, whereas it is decreased in WD-fed mice. Furthermore, the enrichment rate of cardiac triglycerides with long-chain fatty acids is lower at 20 weeks of WD treatment compared with control mice fed the chow diet and becomes even lower by week 24. These changes are associated with decreased triglyceride lipolysis, which corroborates the observed changes in the expression of enzymes that control intracellular triglyceride hydrolysis and avail stored fatty acids for oxidation. This is an important observation, which suggests that lipid droplets in the hearts of WD-fed mice gradually reach a saturation stage, likely because of continuous fatty acid oversupply, that slows down the incorporation of fatty acids into triglycerides. Concurrently, cardiac

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The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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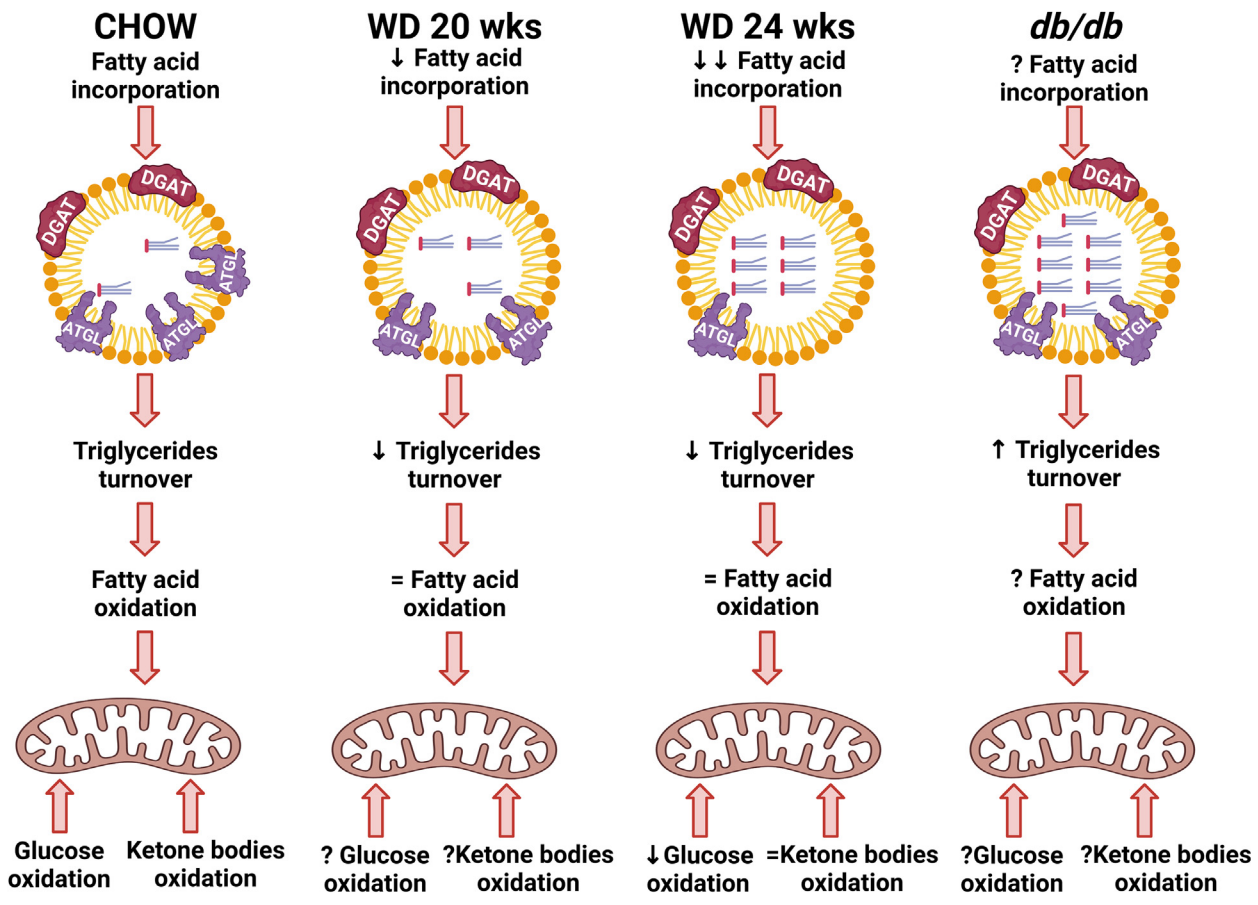
FIGURE 1 Summary of Findings on Cardiac Triglyceride Dynamics



Summary of findings of the study by Maurya et al[1] on cardiac triglyceride dynamics in C57BL/6 mice that were fed with chow diet, western diet (WD) for 20 weeks, or WD for 24 weeks and leptin receptor–deficient (*db*/*db*) mice fed on chow diet. An **upward arrow** denotes an increase, a **downward arrow** denotes a decrease, and an **equals sign** denotes no change compared with chow-fed C57BL/6 mice **(first column)**. The **question mark** indicates parameters that future studies may explore. This figure was created using BioRender.com. ATGL = adipose triglyceride lipase; DGAT = diacylglycerol-acyl transferase.

triglyceride turnover rate in mice fed with WD, although lower compared with that in control mice fed on chow, remains unchanged between mice that are on the WD for either 20 or 24 weeks. The differences in triglyceride turnover between WD-fed wild-type mice and chow-fed *db*/*db* mice warrant future studies to explore whether altered turnover affects the rate of fatty acid incorporation into the intracellular triglyceride pool. Moreover, it needs to be addressed whether lower incorporation diverts fatty acids to other cardiac lipotoxicity pathways, such as ceramide biosynthesis. Slower incorporation of fatty acids may also be accompanied by accumulation of diacylglycerols, which are also toxic for cardiac function. As both ceramides and diacylglycerols activate PKC signaling that interferes with β-adrenergic receptor function and PKA signaling, which affects activation of triglyceride lipases, these concepts would be useful to be tested in the light of the induction or suppression of the cardioprotective diacylglycerol-acyl transferase (DGAT) 1 and adipose triglyceride lipase (ATGL) that control triglyceride and lipid droplet dynamics.

Interestingly, Maurya et al[1] report that ATGL expression is suppressed with WD, and so is the expression of the coactivator of ATGL, CGI-58, whereas expression of ATGL's inhibitor, G0S2, is increased and DGAT1 is not significantly affected. Notably, these changes are not accompanied by alterations in PPARα activation, which this group has shown to rely on fatty acids that are released from triglycerides.[2] Accordingly, the expression of PPARα

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target genes and the levels of fatty acid oxidation do not change, which also points to unchanged PPARα activity. This observation indicates another parameter that separates this mouse model from other types of cardiac stress, such as pressure overload, which this group has studied in the past, showing significant suppression of PPARα activation due to lower intracellular triglyceride turnover.[2] The interplay between intracellular triglyceride dynamics and modulation of glucose uptake and catabolism, which may then act as a regulatory mechanism for PPARα activation and fatty acid oxidation in the context of the Randle cycle, emerges as an important area of future research studies. Nevertheless, unaltered PPARα activation and fatty acid oxidation in the WD-fed mouse model of the present study is associated with lower glucose oxidation. In contrast, cardiac glucose catabolism is increased in the pressure-overload mouse model in which PPARα activity and fatty acid oxidation are suppressed.

Another interesting finding pertains to the association of the dietary stress of the WD, with reduced contractility and diastolic dysfunction with preserved ejection fraction that emerges between 16 and 20 weeks of WD treatment and precedes systolic dysfunction with reduced ejection fraction that appears 4 weeks later. Although high-fat diet also impairs diastolic function prior to the onset of systolic dysfunction,[3] it remains to be explored if modification of the WD constituents or conditions of the treatment may prolong diastolic dysfunction and the duration of heart failure with preserved ejection fraction (HFpEF). If this proves to be the case, another HFpEF mouse model may be added in the panel of animal models for studying this puzzling type of cardiac dysfunction besides the presently most accepted model.[4]

Furthermore, the study proposes that WD-induced cardiomyopathy presents a distinct cardiometabolic phenotype, which differs from those reported in rats fed a high-fat diet or rats with pressure overload-driven cardiac hypertrophy that the same group and others[5] have previously reported. As the previous studies were performed in rats and some comparisons in the present study were made between chow-fed *db*/*db* mice and WD-fed C57BL/56 mice, it is worth studying in the future whether a high-fat diet and the WD have distinct effects in the cardiac triglyceride dynamics of *db*/*db* mice. This would clarify whether the important observations of the present study can be attributed to unique features of the WD or inhibition of leptin signaling in the *db*/*db* mice.

In conclusion, the study by Maurya et al[1] adds important pieces of knowledge that are useful for the optimization of mouse models for cardiometabolic diseases. The study both provides answers and generates important new questions that future studies will be needed to address, including exploration of both female and male mice and investigation of potential differences in cardiac triglyceride dynamics in other mouse models of diet-induced cardiomyopathy, cardiac lipotoxicity, and HFpEF. Overall, this is an important contribution to the field that adds on existing findings, which highlight the critical role of triglyceride dynamics for metabolic remodeling of cardiomyocytes and the onset of diet-induced cardiomyopathy.

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