

Impact of High-Fat Diet Composition on Obesity Development and Cagrilintide Response in NTac:SD Rats

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Background and Aims

Diet-induced obesity (DIO) rat models are increasingly used for obesity research, particularly for targets such as amylin analogs that show limited efficacy in mice. 60% kcal fat diets are standard for DIO mice, optimal fat content for rats remains debated due to feeding behavior and tolerance. This study aimed to (1) compare obesity development in NTac:SD rats fed 45% vs 60% kcal fat diets, and (2) evaluate the weight and metabolic responses to cagrilintide, a long-acting amylin analog.

Methods

NTac:SD rats (Taconic Biosciences) were initiated on either a 45% or 60% kcal fat diet (D12451 or D12492 from Research Diets, respectively) at 6 weeks of age and maintained for 15 weeks prior to shipment to the study site. Following 1 week of acclimation, animals were randomized to receive vehicle or cagrilintide, once daily for 14 days. The 45% fat cohort received two doses (10 or 30 nmol/kg/d), while the 60% fat cohort received only 10 nmol/kg/d. Body weight and metabolic parameters were assessed throughout.

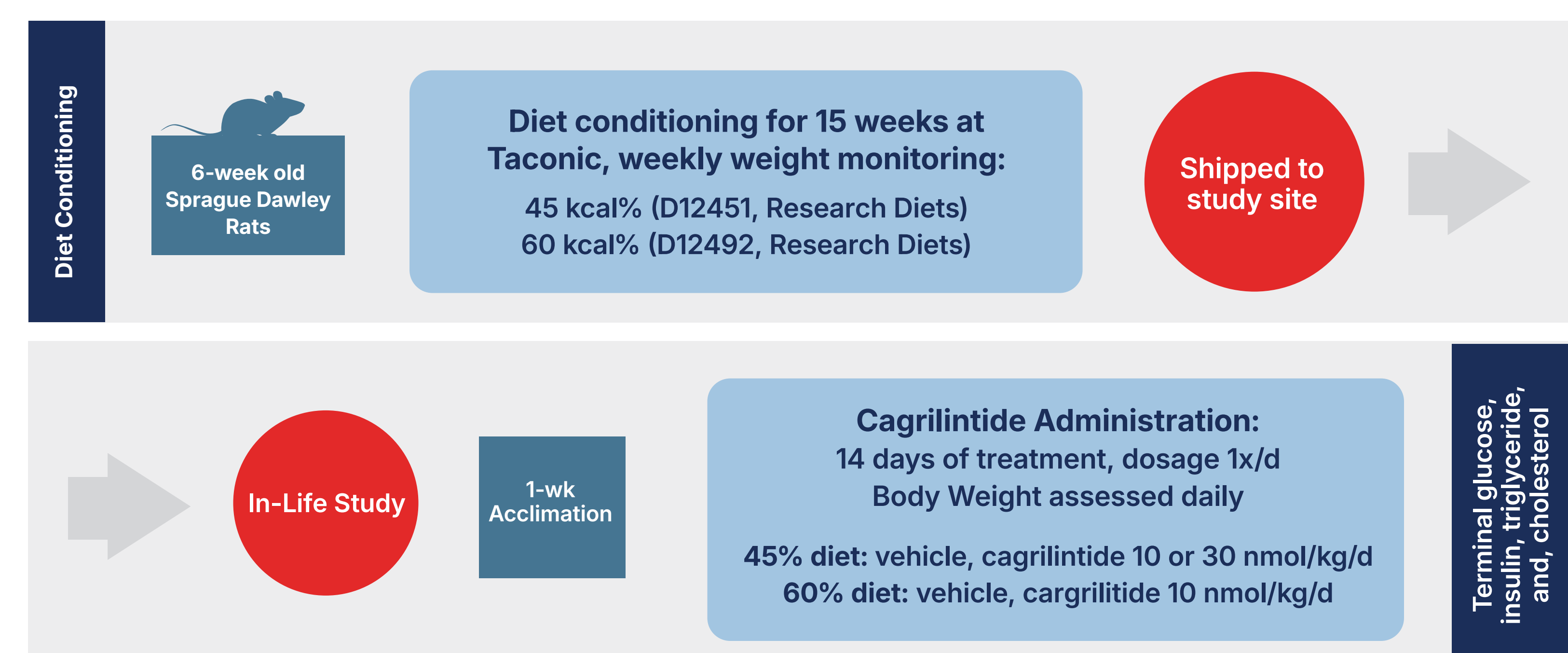


Figure 1. Overview of animal cohorts and experimental timeline.

DIO Series 2013

Product Number	D12451		D12492	
	gm%	kcal%	gm%	kcal%
Protein	24	20	26	20
Carbohydrate	41	35	26	20
Fat	24	45	35	60
Total		100		100
gm/kcal%	4.73		5.24	
Ingredient	gm	kcal	gm	kcal
Casein, 30 Mesh	200	800	200	800
L-Cystine	3	12	3	12
Corn Starch	72.8	291	0	0
Maltodextrin 10	100	400	125	500
Sucrose	172.8	691	68.8	275
Cellulose, BW200	50	0	50	0
Soybean Oil	25	225	25	225
Lard	177.5	1598	245	2205
Mineral Mix S10026	10	0	10	0
DiCalcium Phosphate	13	0	13	0
Calcium Carbonate	5.5	0	5.5	0
Potassium Citrate, 1 H2O	16.5	0	16.5	0
Vitamin Mix V10001	10	40	10	40
Choline Bitartrate	2	0	2	0
FD&C Red Dye #40	0.05	0	0.05	0
FD&C Blue Dye #1	0.05	0	0.05	0
Total	904.05	4057	773.85	4057

Table 1. Formulations for high fat diets used to induce obesity in NTac:SD rats

Results

Both diet groups exhibited comparable weight gain during the induction phase, with no significant differences between 45% and 60% fat diets. Cagrilintide rapidly reduced body weight in all treatment groups, with a dose-dependent effect in the 45% fat cohort in which the 30 nmol/kg group achieved significantly greater weight loss. At 10 nmol/kg, cagrilintide reduced ambient glucose in both diet groups and lowered insulin only in the 45% fat cohort. Total triglycerides decreased in the 45% fat group at both doses, while cholesterol remained unchanged.

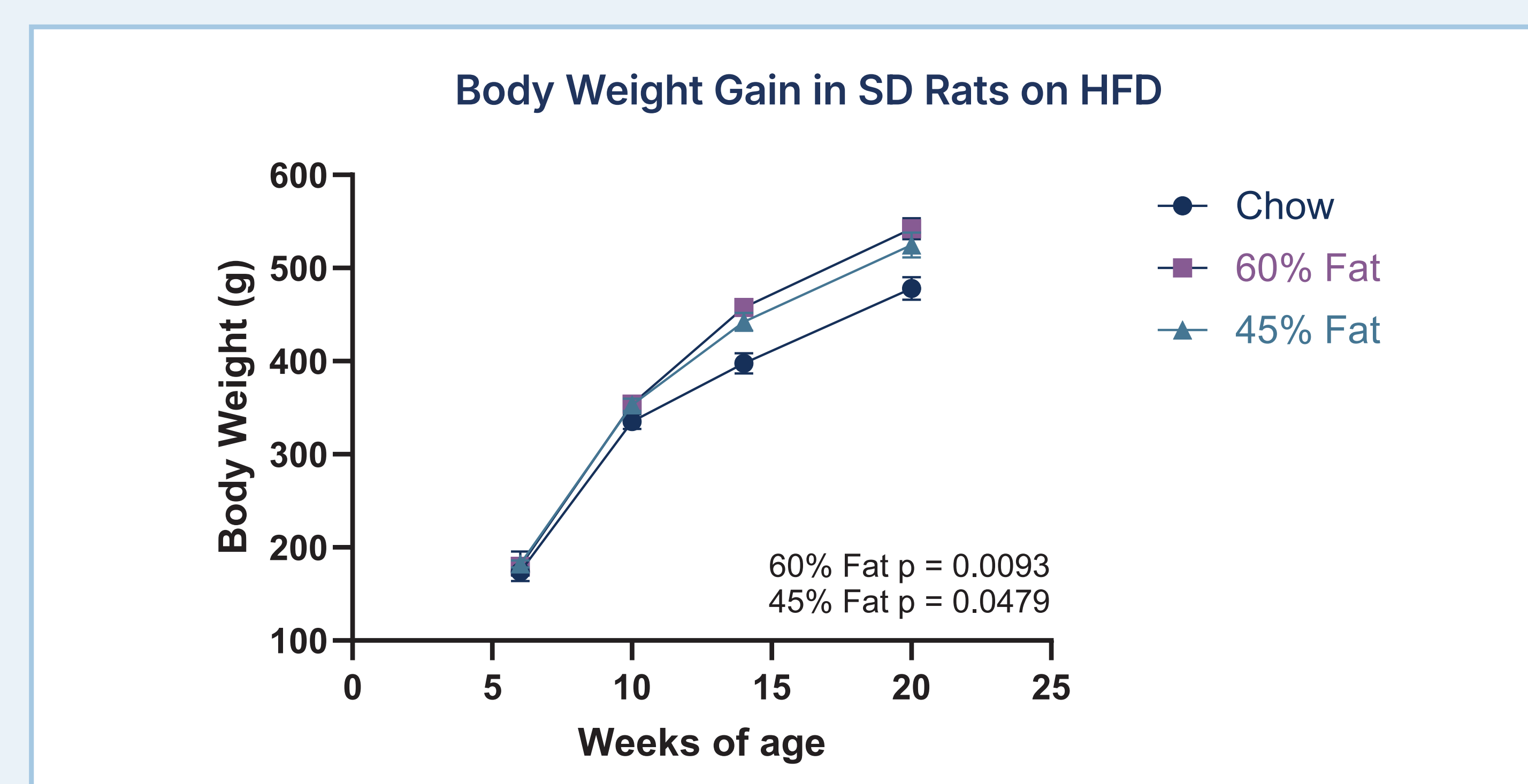
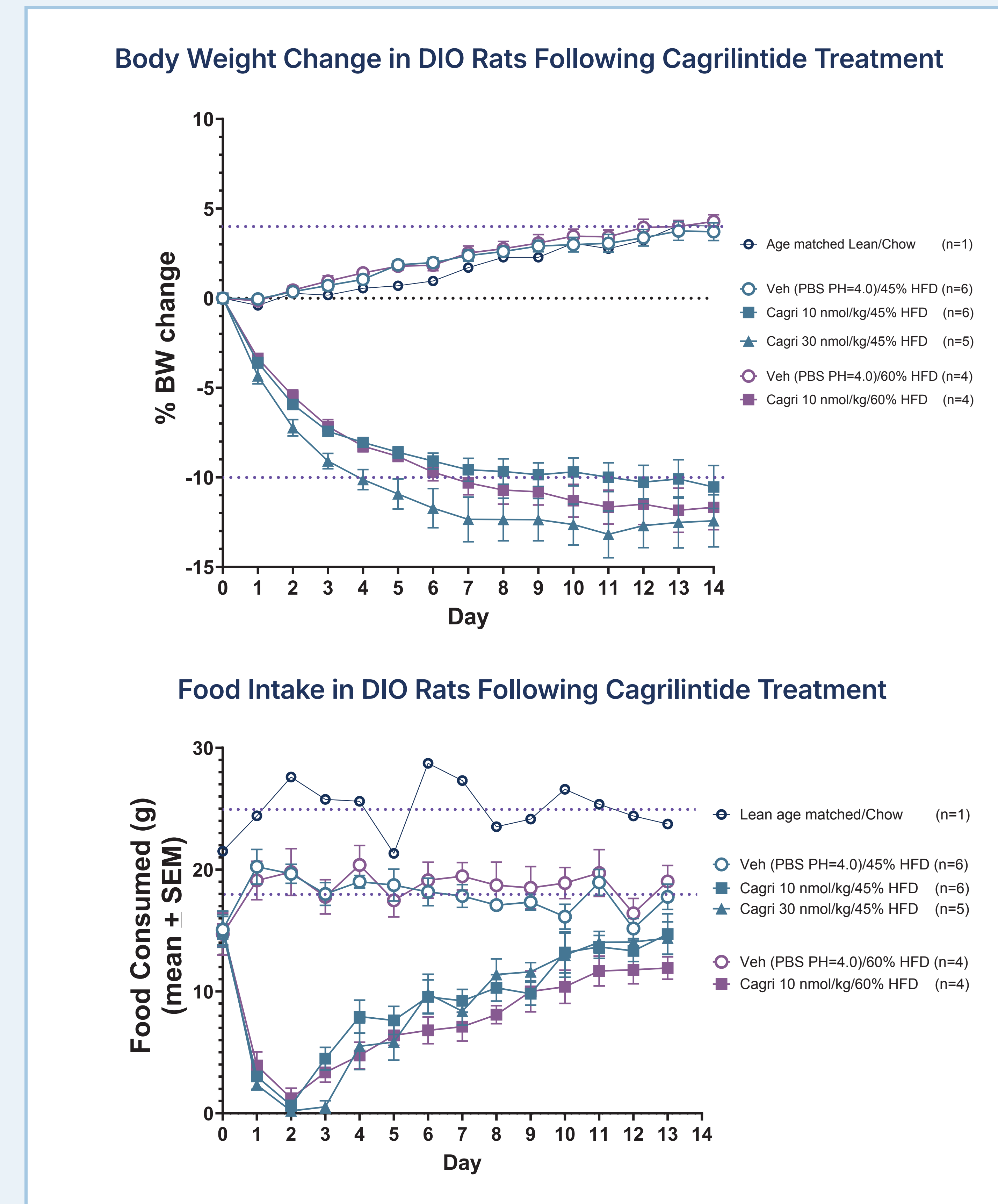


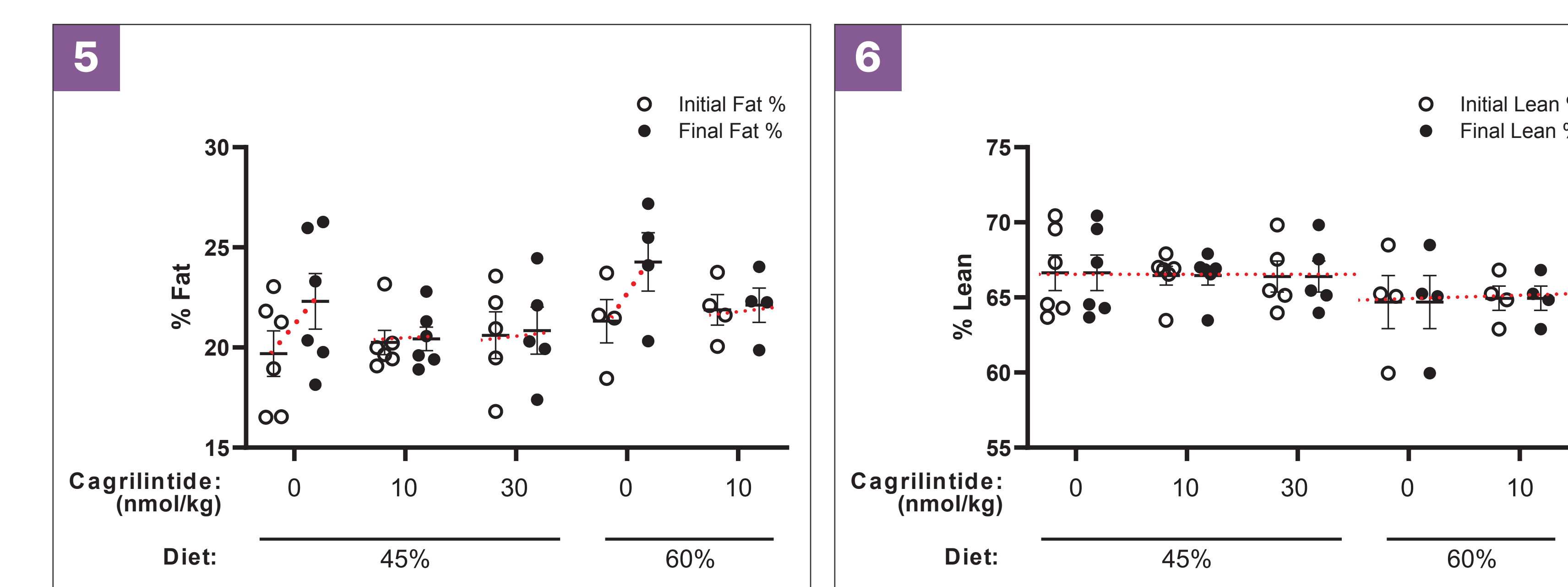
Figure 2. NTac:SD rat growth curves when fed control chow, 45% fat diet (D12451), or 60% fat diet (D12492) prior to shipment to study site. Rats on 45% fat and 60% fat diets gained significantly more weight than rats fed control chow by 2-way ANOVA with Dunnett's multiple comparisons test.



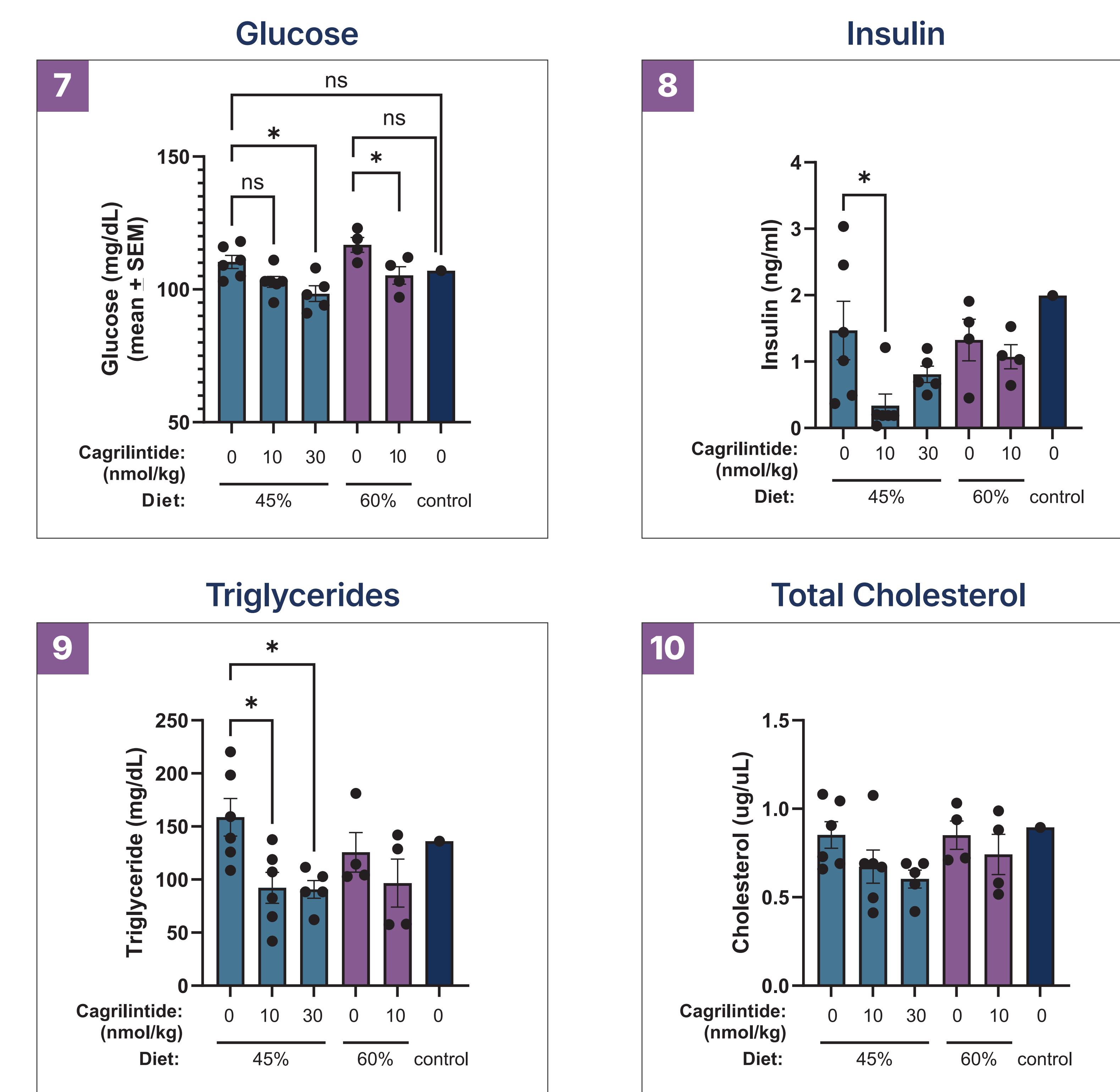
Figures 3 and 4. Change in body weight and food consumption of DIO rats in response to cagrilintide treatment.

Results (Continued)

Changes in Fat and Lean Mass Following Cagrilintide Treatment



Figures 5 and 6. Changes in body composition of DIO rats treated with Cagrilintide. %Fat continued to increase in control groups. Cagrilintide treatment did not reduce lean mass.



Figures 7-10. Serum metabolites in DIO rats treated with Cagrilintide following a 5 hr fast.

Conclusions

- ▶ **NTac:SD rats** develop robust obesity on both 45 and 60% HFD formulas
- ▶ **Cagrilintide demonstrated** potent weight-reducing effects, while preserving lean muscle and preventing further fat deposition
- ▶ **Ambient glucose levels** were reduced by cagrilintide treatment in both diet arms
- ▶ **Insulin and cholesterol** responses varied with diet, suggesting that diet selection may be relevant in targeting metabolic effects beyond weight loss

