The key to weight loss maintenance:

Exploring mechanisms of metabolic adaptation in a Göttingen Minipig model of obesity

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Metabolic adaptation

- Metabolic adaptation is the body's response to changes in diet, exercise, or hormonal levels, aimed at maintaining energy balance. This can result in the body becoming more efficient at using fewer calories to perform the same tasks, which can make weight loss more challenging over time[1].

Overall aim

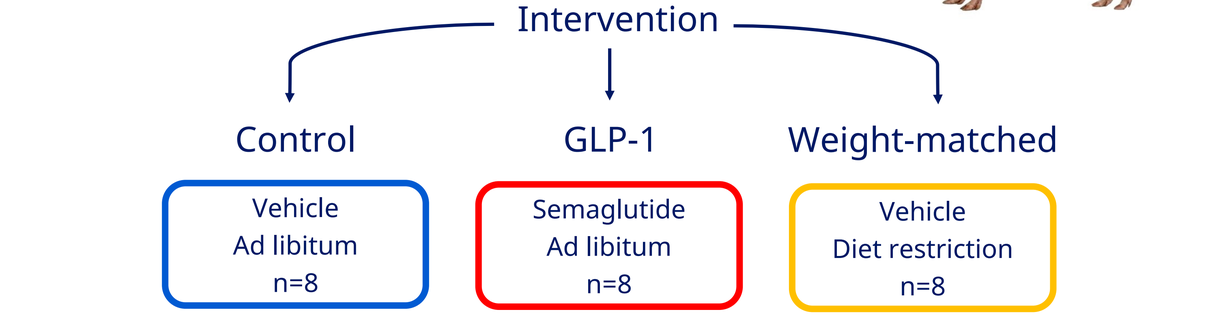
- Establish new knowledge on how metabolic adaptation is regulated in obesity, with the aim to propose novel targets for pharmacologically induced reversal of the metabolic adaptation.

Hypotheses

- Obese Göttingen Minipigs displaying similar metabolic changes as humans when subject to a weight loss
- The metabolic adaptation is associated with:
  1) differential gene expression
  2) differential regulation of neuroendocrine pathways
  3) differential levels of circulating biomarkers
- The metabolic adaptation is larger for a dietary restriction as compared to pharmacological treatment with a GLP-1 analogue

Methods

- 24 Female DIO Göttingen Minipigs, 1.5-year-old



- Study outline

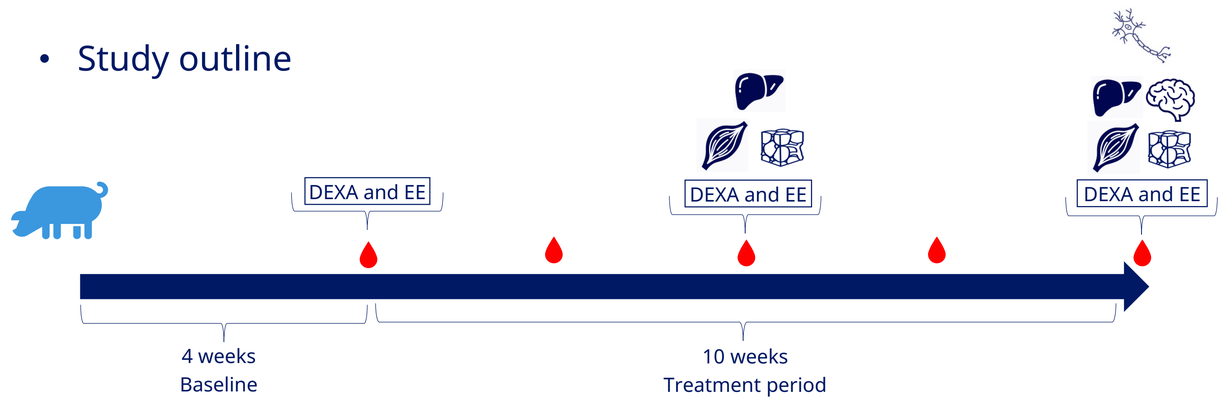


Figure 1: Study outline. DEXA: Dual-Energy X-ray Absorptiometry. EE: Energy expenditure by indirect calorimetry. Tissue symbol represent biopsies after 5 weeks and tissue harvest at terminal necropsy. Blood samples at 5 timepoints throughout the study.

Results

Food intake

"Semaglutide decreased food intake by 44%"

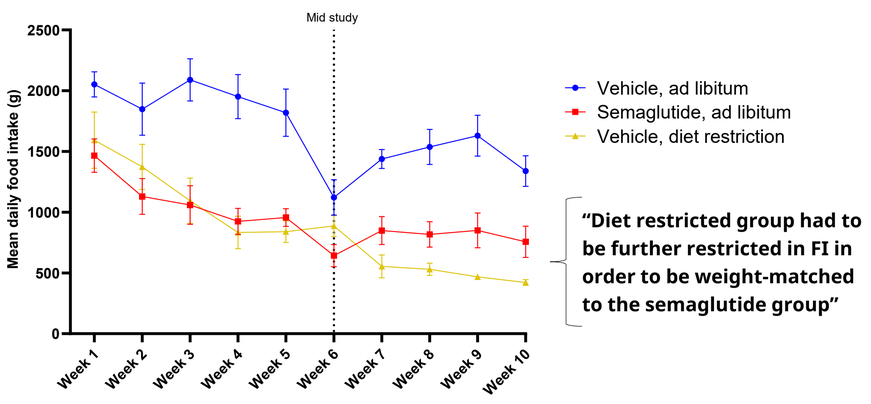


Figure 2: Daily mean food intake per group calculated on weekly basis (gram/day). All pigs fed a high fat diet. Graph represent mean±SEM (n = 8).

Body composition

"Semaglutide improved body composition"

*DEXA scanner

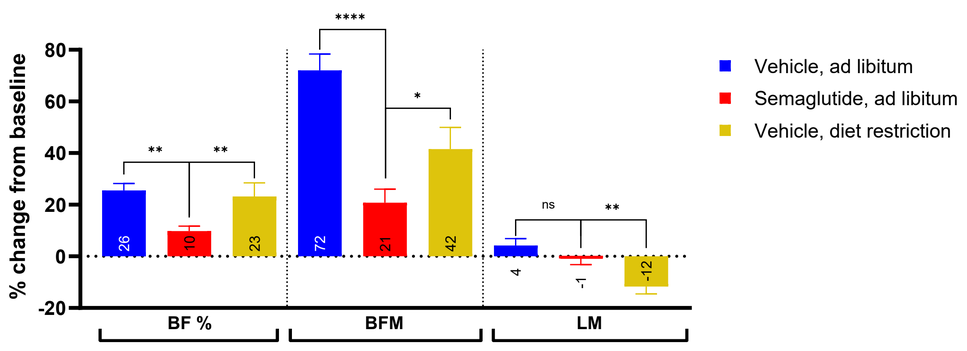


Figure 4: Body composition change from baseline (in % change). BF %: body fat percentage. BFM: total body fat mass. LM: lean mass. Bar plot represent mean±SEM (n = 8). Statistically significance was determined by Two-way ANOVA with Tukey's multiple comparisons. Ns: not significant, *:p<0.05; **: p<0.01, ****: p<0.0001.

Body weight

"Weight-matching was successful, but all groups gained weight"

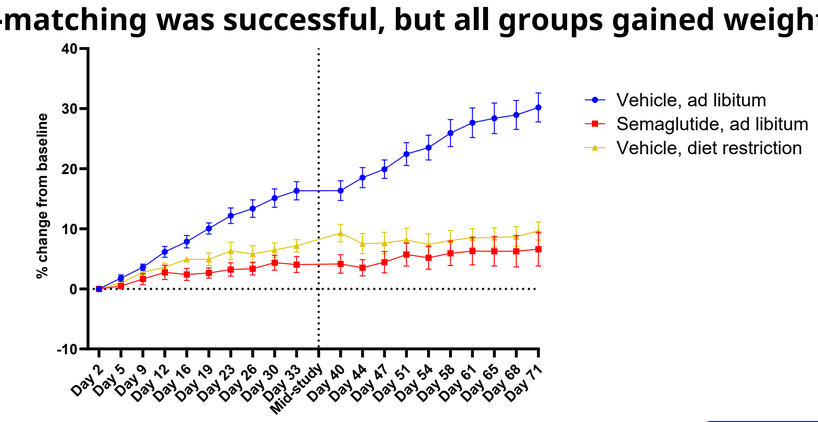
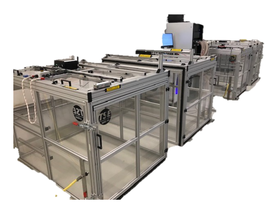


Figure 3: Body weight change from baseline (in % change). Graph represent mean±SEM (n = 8).

Energy expenditure

"Diet restriction decreased energy expenditure – and more so than semaglutide despite same BW change"



*Metabolic chambers

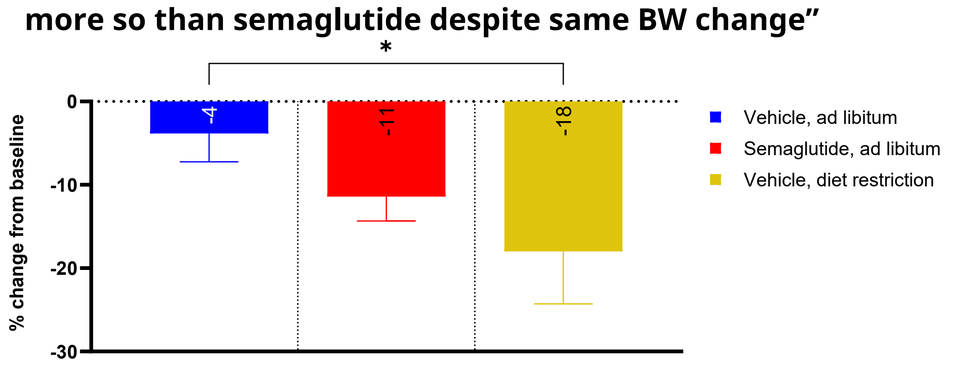


Figure 5: Energy expenditure change from baseline (in % change). Bar plot represent mean±SEM (n = 8). Statistically significance was determined by Two-way ANOVA with Tukey's multiple comparisons. *:p<0.05;

Preliminary Conclusion

The data indicates that metabolic adaptation was observed in the minipigs, with a greater magnitude seen in the diet restricted group compared to the semaglutide treated group.

What's next?

Purpose	DEG´s associated with MA	Changes in blood parameters	Adipose tissue adaptation
Method	Bulk RNA-sequencing, scRNA-seq and ISH	Biochemistry, hormones, miRNA, proteomics etc.	Lipolysis capacity test, WB, NE content and inflammation
Tissue/ Blood			

Aim

"**Discover mechanisms or pathways** causing metabolic adaptation that could potentially become **targets for novel anti-obesity medication** enabling weight loss maintenance."

DEG´s: differentially expressed genes, MA: metabolic adaptation, scRNA-seq: single cell RNA sequencing, ISH: In Situ Hybridization, NE: norepinephrine, WB: Western blot

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[1] Martínez-Gómez et. Al. Journal of Strength and Conditioning Research 36(10):p 2970-2981, October 2022. Metabolic Adaptations to Weight Loss: A Brief Review. DOI: 10.1519