Deciphering the Gut-Joint Axis
Pioneering New Therapeutic and Preventive Strategies for Obesity

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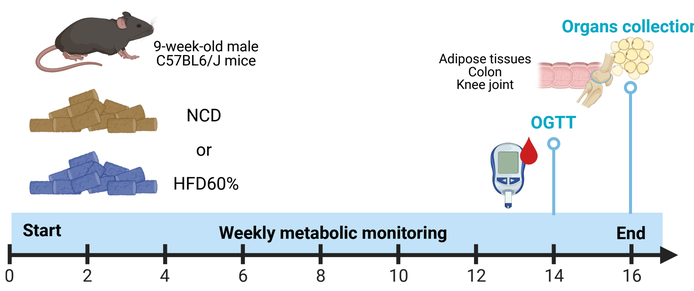
INTRODUCTION

In the context of the increasing prevalence of obesity and its comorbidities, understanding the interactions between the gut and joints is becoming crucial. Enterosys, a specialist in gut-peripheral organ communication, in collaboration with Atlantic Bone Screen, an expert in preclinical research in bone and joint pathologies, offers an integrated service to study the gut-joint axis. This innovative approach aims to explore the therapeutic potential of new compounds in the treatment of osteoarticular pathologies associated with obesity. To do so, various parameters were evaluated: metabolic (weight gain, oral glucose tolerance test, adipose tissue weight), intestinal (barrier function markers and permeability, histological analyses) and articular (morphological analyses by microtomography (µCT) and histopathological analyses).

METHODS

Animals were maintained to an acclimatization period of 5 days after their arrival. The animals were housed in ventilated and enriched cages in Specific Pathogen Free (SPF) conditions. Mice were housed in groups of 5 animals on a normal light cycle, 22 ± 2 °C and 50 ± 10% relative humidity. During the experimental phase (16 weeks), High Fat Diet 60% (HFD, Research Diet) or Normal Chow Diet (NCD, Safe) and tap water were provided *ad libitum*.



Effects of a high fat diet on knee joint structure was evaluate by histopathological scoring performed by a Board-certified pathologist, according to the OARSI (Osteoarthritis Research Society International) guidelines on Toluidine Blue (TB) for cartilage and Hematoxylin-Eosin-Saffron (HES)-stained frontal sections of the right knee. Microtomography (µCT) analysis of joints to allow the detection and characterization of cartilage degeneration and abnormal bone adaptations, such as osteophytes, subchondral sclerosis, bone cyst presence.

Extensive Parameter Profiling

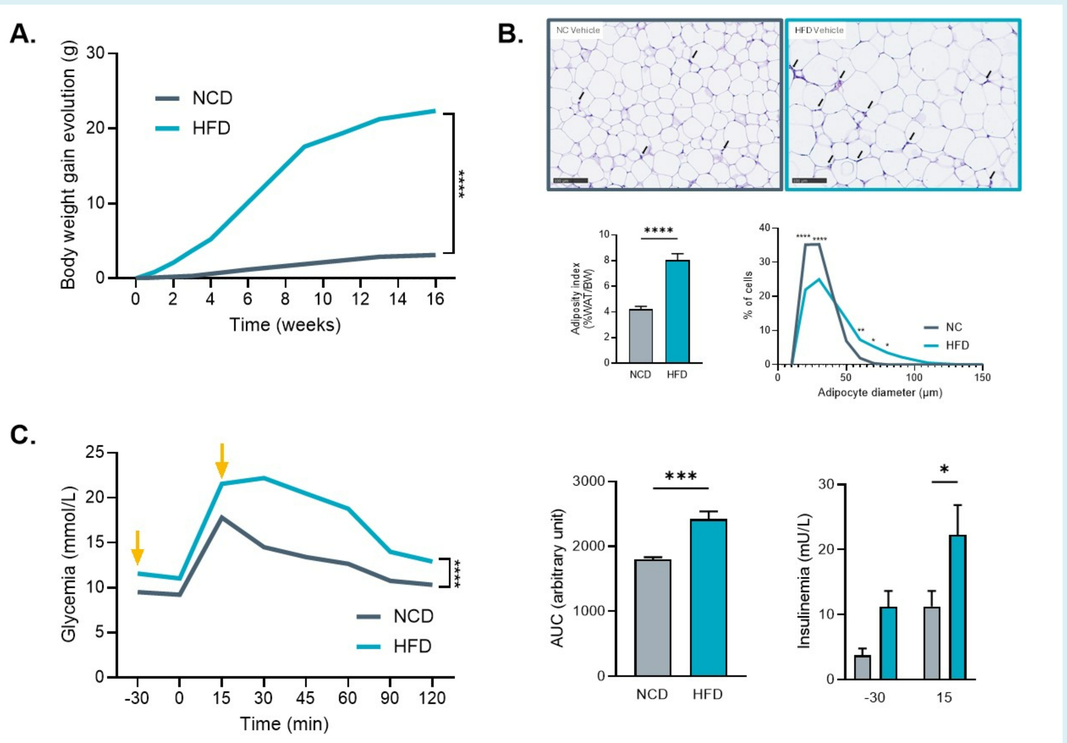
- Body weight management
- Adipose tissue weight
- Oral glucose tolerance test (OGTT)
- Insulin sensitivity
- In-depth adipose tissue histology
- Leaky gut phenotype (permeability & gut barrier function)
- Enteric nervous system activity (# second brain)
- Histopathological analysis of knee joint structure
- Morphological analysis (microtomography)

CONCLUSION

The results show significant changes in metabolic parameters and alterations in intestinal barrier function markers. Slight signs of joint structure alterations were also observed, highlighting the impact of obesity on osteoarticular health.
This study highlights the potential of the gut-joint axis as a therapeutic target in metabolic and degenerative pathologies. Our combined preclinical expertise will provide a comprehensive solution for evaluating the efficacy of compounds in a preclinical setting, promoting a holistic approach to managing obesity and its joint comorbidities.

RESULTS

FIGURE 1:
Metabolic phenotyping.
Effects of a high fat diet (HFD) on **(A)** body weight gain over time; **(B)** Representative images of subcutaneous adipose tissue sections with Hematoxylin-Eosin staining, adiposity index and adipocytes diameter and distribution analysis (scale bars, 100µm). Arrows represents immune cells infiltration; **(C)** glycemia regulation before and after an oral load of glucose (2g/kg of body weight), the average area under the curve (AUC) and insulinemia at t-30min and t+15 min the oral load of glucose, n=8-10 per group. The associated table below described p values obtained 2-way ANOVA followed by Bonferroni's post hoc test or a t-test, *p < 0.05, **p < 0.01,***p < 0.001, ****p < 0.0001 NCD *vs* HFD.



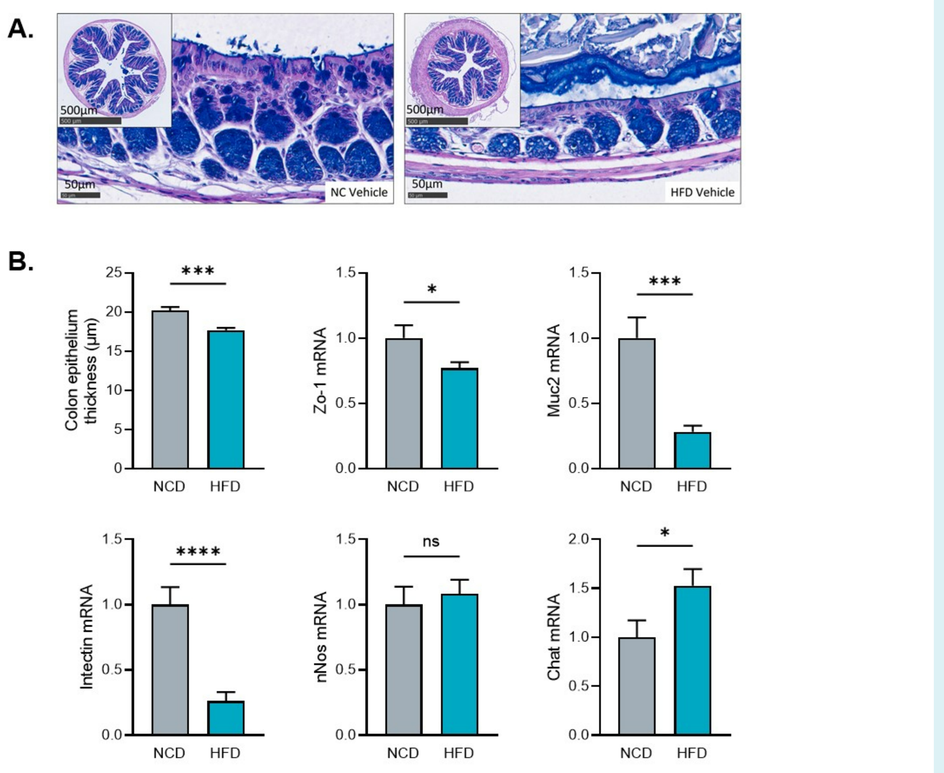


FIGURE 2:
Intestinal phenotyping.
Effects of a high fat diet (HFD) on **(A)** Colonic epithelium layer thickness. Representative images of colon sections with alcian blue staining and epithelium thickness analysis (scale bars, 50 and 500µm), **(B)** Epithelium integrity and gene expression of intestinal barrier biomarkers in the colon *Zo-1* mRNA relative expression, biomarkers of intestinal tissue integrity *Muc2* and *Intectin* mRNA relative expression, biomarkers of enteric nervous system activity *nNos* and *Chat* mRNA relative expression. n=8-10 per group. The associated table below described p values obtained with a t-test, *p < 0.05, ***p < 0.001, ****p < 0.0001 NCD *vs* HFD.

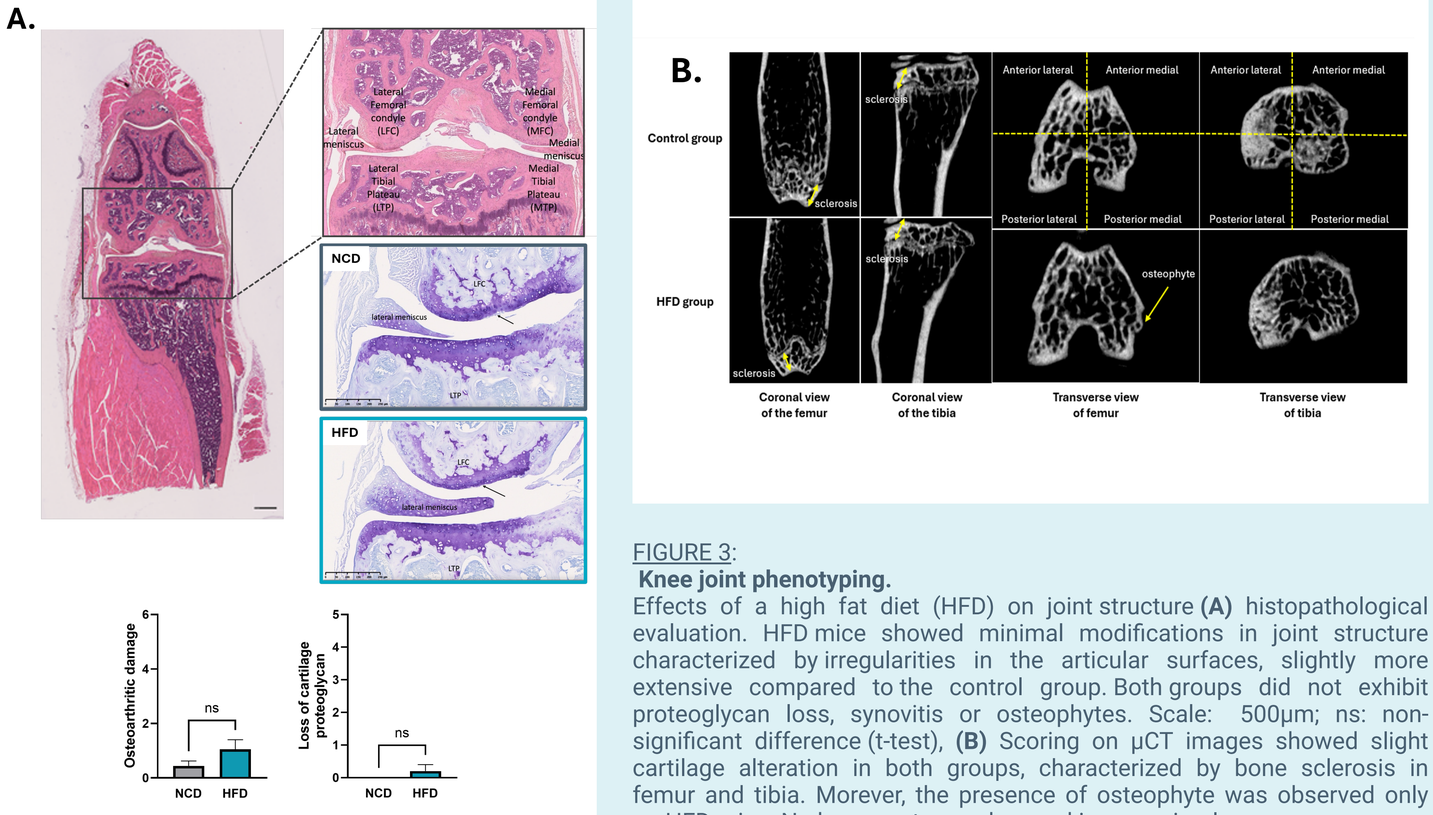


FIGURE 3:
Knee joint phenotyping.
Effects of a high fat diet (HFD) on joint structure **(A)** histopathological evaluation. HFD mice showed minimal modifications in joint structure characterized by irregularities in the articular surfaces, slightly more extensive compared to the control group. Both groups did not exhibit proteoglycan loss, synovitis or osteophytes. Scale: 500µm; ns: non-significant difference (t-test), **(B)** Scoring on µCT images showed slight cartilage alteration in both groups, characterized by bone sclerosis in femur and tibia. Morever, the presence of osteophyte was observed only on HFD mice. No bone cyst was observed in any animals.

Contact

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