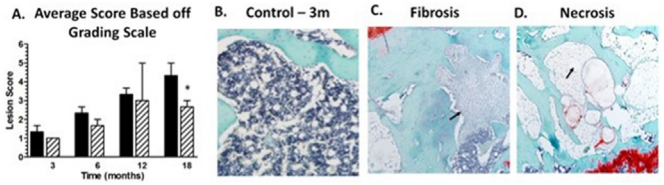

Figure 2: Histological analysis of bone marrow lesions in Hartley guinea pigs. A – Graphical representation of average grade assigned based off of grading scale. B – Photo of bone marrow of a control animal at 3 months, C and D are examples of found bone marrow lesions. C – Fibrosis (black arrow). D – Encapsulated (red arrow) and non-encapsulated (black arrow) necrosis.

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STUDY OF THE EVOLUTION OF THE OSTEOARTHRITIS PATHOLOGY AND THE MECHANICAL PROPERTIES OF CARTILAGE IN A SPONTANEOUS OSTEOARTHRITIS MODEL IN THE DUNKIN-HARTLEY GUINEA PIGS

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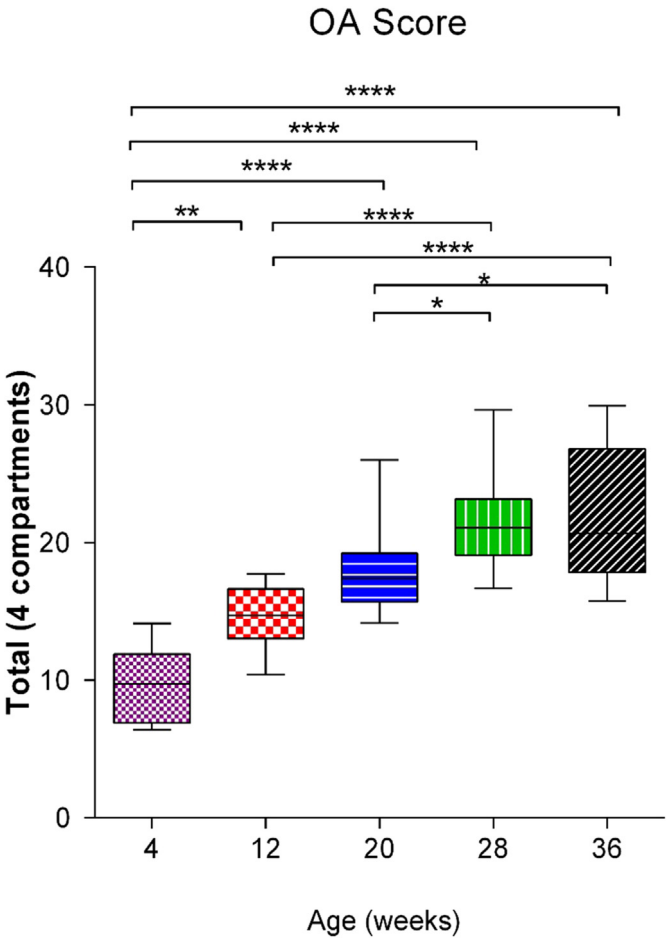
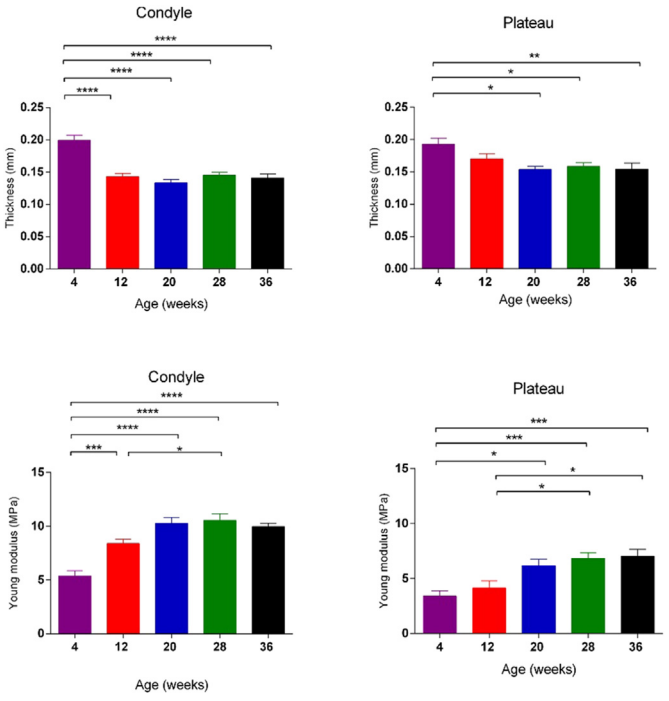
Purpose: In animal models, the severity of cartilage damage is assessed by histological scores evaluating the structure, the proteoglycan content, the integrity of the tidemark, the cellularity, and osteophytes. In parallel to these histological analyzes, we studied the mechanical properties of cartilage at different stages of disease progression in the Dunkin-Hartley guinea pigs. We also correlated the severity of histological lesions with the mechanical properties of cartilage.

Methods: Sixty, male, 3-week-old Dunkin-Hartley guinea pigs from Charles River Laboratories (Paris, France) were used. Guinea pigs were randomized into 5 groups of 12 guinea pigs. At 4-week-old and every 8 weeks until week 36, twelve Hartley guinea pigs were sacrificed. Histological severity of the lesion was evaluated using OARSI score and mechanical properties of cartilage were assessed by the MACH-1 technology (Biomomentum, Canada). To do this, the tibial plateaus and femoral condyles of 60 guinea pigs were taken. An indentation protocol and measurement automated thickness was applied to cover the entire articular surface. The Young modulus (measure of the stiffness of the cartilage) and the thickness were calculated using the Mach-1 Analysis software.

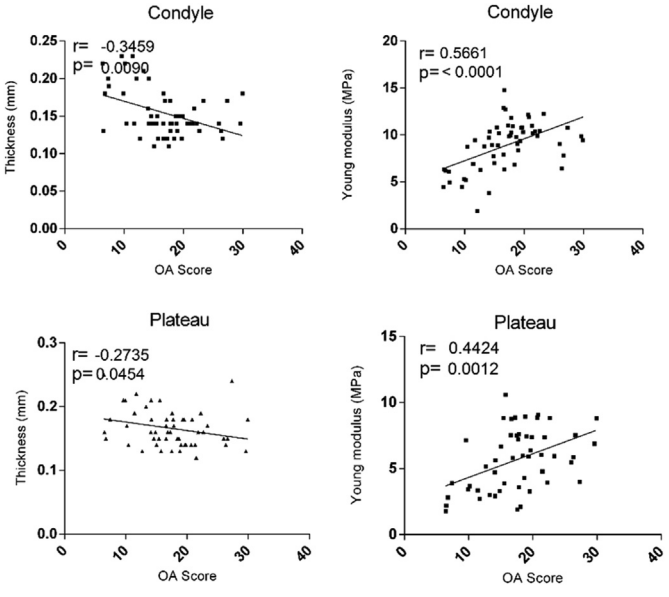
Results: Histological assessment of cartilage lesions showed that guinea pigs spontaneously developed severe knee osteoarthritis. In all animals, the global histological score increased significantly with age until week 28 ($p < 0.0001$ between week 4 and 28) and then stabilized (between weeks 28 and 36).



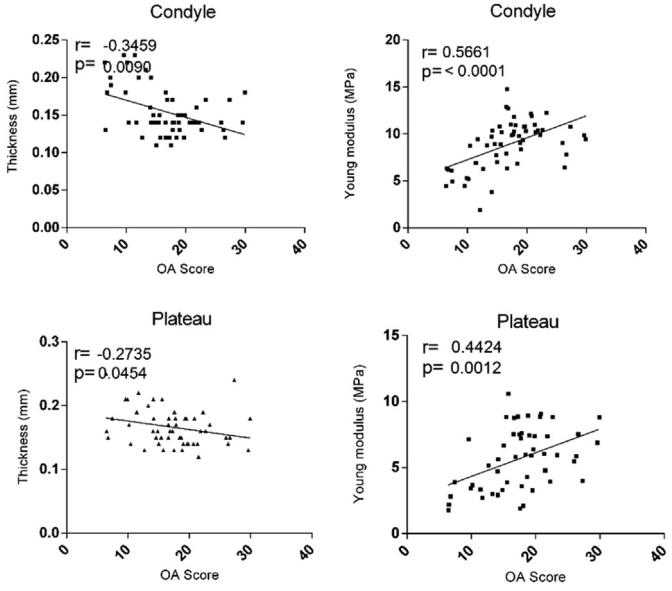
Significant differences in thickness and young modulus between groups over time were observed.



The cartilage thickness gradually decreased until week 20 and then remained stable between weeks 28 and 36. A significantly positive correlation was observed between the global OARSI histological score and the young modulus (condyle: $r = 0.566$, $p < 0.0001$; tibial plateau: $r = 0.442$, $p < 0.0012$).



When histological items were analyzed individually, it appears that the structure of the cartilage and the proteoglycan content were better correlated with the instantaneous modulus of the femoral condyle ($r = 0.58, < 0.0001$; $r = 0.517$, $p < 0.0001$) than with other items. At the tibial plateaus, the strongest associations were found between the items cartilage structure and integrity of tidemark and the young modulus ($r = 0.435$, $p = 0.0014$; $r = 0.433$, $p = 0, 0015$). Conversely, a significantly negative correlation was also observed between the global histological score and OA cartilage thickness (condyle: $r = -0.346$, $p = 0.009$; plateau: $r = -0.273$, $p = 0.045$).



Conclusions: As expected, the global histological score increased significantly with the age of the animals. We also showed a correlation between the instantaneous modulus and the severity of the histological lesions of the cartilage. These observations show the interest to study the mechanical properties of cartilage in animals. The mechanical parameters give additional information on the articular cartilage quality.

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DIET-INDUCED OBESITY, SYSTEMIC INFLAMMATION, AND THE DEVELOPMENT OF HIP AND SHOULDER OSTEOARTHRITIS: INSIGHTS FROM A RAT MODEL

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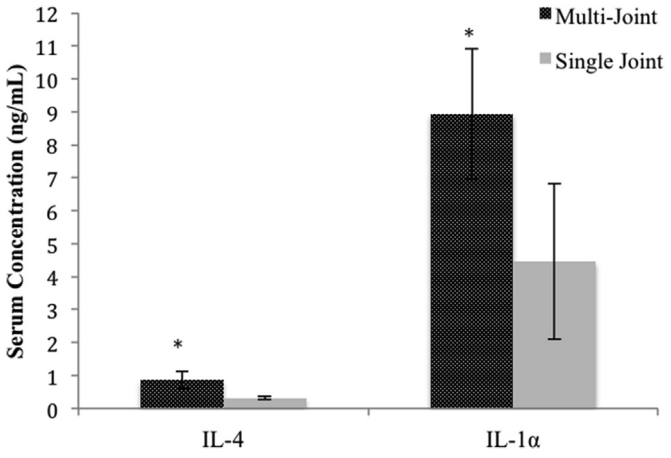
Purpose: Obesity is one of the primary risk factors for the onset and progression of osteoarthritis (OA). Using a rat model of high-fat/high-sucrose (HFS) diet-induced obesity (DIO), we have demonstrated a strong significant relationship between body fat, systemic inflammatory mediators, and knee OA, using a Modified Mankin scoring system. Although several studies demonstrate a relationship between obesity and hand OA, the relationship between body fat, systemic inflammatory mediators, and structural OA-like changes in other synovial joints, like the shoulder and hip, is inconsistent. The purpose of this study was to determine whether HFS-induced obesity would result in OA-like changes in the shoulder and hips of rats. It was hypothesized that HFS-fed animals would exhibit OA-like changes in the hip and shoulder, and these changes would be associated with elevated serum levels of systemic inflammatory mediators.

Methods: Sixteen 12-week old male Sprague-Dawley rats were allocated to either an HFS diet (DIO, 40% fat, 45% sucrose, n=9) or chow diet (13% fat, 0% sucrose, n=7) for a 12-week obesity induction period. After the obesity induction period, body mass, and composition (Dual Energy X-ray Absorptiometry) were quantified, and animals were euthanized. Shoulder (humeral and scapular cartilage) and hip (femoral and acetabular cartilage) joints from all animals were harvested, fixed in formalin, and scored using the Mankin criteria. OARSI subscores for bone changes and synovitis were also determined for each joint. Serum inflammatory mediators were profiled using a 27-plex Luminex ® assay. Outcomes were compared by diet using a one-way ANOVA or non-parametric statistics (Mankin and OARSI scores) at α=0.05. Relationships between body fat, body mass, systemic inflammatory mediators, and joint damage were evaluated using Spearman correlations.

Results: DIO animals gained significantly more body mass (p=0.002) and body fat (p<0.001) compared to chow. Although a variety of pro-inflammatory mediators were increased in the serum from DIO animals, histological scores were statistically similar between DIO and chow animals (Table 1, p>0.05). No significant relationships were found between body mass or body fat and damage in hip and shoulder. Serum leptin, however, was positively associated with increased hip synovitis scores across all animals (R=0.57, p=0.02) and a number of mediators were positively associated with increased acetabular cartilage damage (IL-4, IL-5, IL-13, IL-17; $R \geq 0.50$, $p \leq 0.05$). No significant positive relationships were calculated between any measure of OA damage at the shoulder and serum inflammation. Of note, an increased number of DIO animals had OA damage in both the shoulder and hip compared to chow animals (multi-joint: 4/9 DIO animals, 1/7 chow animals). When compared to animals with damage at only one joint site, animals with multi-joint OA had significantly more histological damage, increased shoulder synovitis (p<0.05) a trend toward increased hip synovitis (p=0.13), and increased serum levels for IL-1α and IL-4 (Figure 1, p<0.05).

Conclusions: Hip and shoulder joints do not consistently sustain OA damage after 12-weeks of DIO in rats, potentially due to the known genetic heterogeneity of these rats, refuting our primary hypothesis. However, systemic inflammatory alterations resulting from DIO induction in this model system may lead to a higher incidence of multi-joint OA with the HFS diet over the long term. Future work will evaluate whether OA develops more slowly in hip and shoulder joints when compared to previous reports in DIO knee joints, possibly due to the unique environment of the knee (i.e. Hoffa's fat pad, presence of menisci, hinge joint configuration). However, potential links between DIO, systemic inflammation, synovium changes and OA-like alterations in the hips and shoulders of DIO rats were identified, and these links will be further investigated over longer time periods.



Shoulder and Hip OA-like Changes for Obese and Chow Animals.

Group	Shoulder Joint			Hip Joint		
	Humerus	Scapula	Synovitis	Femur	Acetabulum	Synovitis
Chow	2 (2–14)	–	0 (0–4)	3 (2–13)	4 (0–6)	0 (0–1)
DIO	2 (2–14)	0 (0–14)	0 (0–2)	2 (0–14)	2 (0–14)	0 (0–1)
Single-Joint OA	2 (2–11)	–	0 (0–1)	2 (0–10)	2 (0–6)	0 (0–1)
Multi-Joint OA	14 (10–14)*	0 (0–14)	0 (0–4)*	5 (0–14)ˆ	7 (5–14)*	0 (0–1)ˆ

Data are shown as median (minimum-maximum); *indicates p<0.05 compared to single-joint OA group; ˆindicates p<0.15 compared to single-joint OA group