Investigating the Impact of High-Fat High-Sucrose Diet on Hypertrophy and Hyperplasia in the Infrapatellar Fat Pad

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INTRODUCTION: Osteoarthritis (OA), a widely prevalent whole joint disease, primarily presents itself in significant joint structures such as the knee, hand, back, and hip. OA is shown to be closely linked to obesity, implying that joint degeneration could arise from heightened joint loading or systemic inflammation and metabolic issues associated with obesity. Metabolic OA phenotype, which involves OA linked to obesity, is characterized by the presence of large visceral fat deposits that have the potential to release inflammatory cytokines and adipokines, triggering systemic inflammation. The infrapatellar fat pad (IFP), also known as Hoffa's fat pad located near the synovium, has been reported to secrete substantial amounts of inflammatory cytokines and adipokines inside the joint due to the expansion of adipocytes within the IFP, leading to both hypertrophy and hyperplasia. Consequently, the objective was to examine the impact of a high-fat-high-sugar (HFHS) diet on the infrapatellar fat pad (IFP), specifically focusing on hyperplasia and hypertrophy. Furthermore, our aim was to explore potential divergent responses to the diet between males and females, elucidating potential sex-related variations in cell behavior.

METHODS: 12 weeks old male and female Sprague Dawley rats were randomized into two groups. Rats consuming chow diet (chow, n=4) and rats exposed to the HFHS diet (HFS, n=4) were on the diet for a duration of 12 weeks. At 24 weeks, rats knee joints were harvested, fixed in NBF (Neutral Buffered Formalin), and processed in paraffin. 10um sections were cut using a microtome. Slides underwent staining with hematoxylin and eosin, and subsequent imaging occurred using a light microscope. Quantification of cell area and number was performed utilizing ImageJ software. Cellular hyperplasia and hypertrophy were examined and compared within the context of both diet groups and distinct sexes. The assessment of cell hypertrophy involved the quantification of cell area, with comparisons drawn across various intervals: <500μm^2, 500-999μm^2, 1000-1499μm^2, 1500-1999μm^2, 2000-2499μm^2, 2500-2999μm^2, and 3000-3499μm^2.The statistical disparity was evaluated using the Mann-Whitney U test. The study was approved by the University of Calgary's Life and Environmental Sciences Animal Care Committee.

RESULTS SECTION: Imaging analysis and quantification demonstrated no notable hyperplasia discrepancy between rats fed the chow diet and those on the HFHS diet. In the chow group (n=4), adipocyte count in the IFP was 54,679, while in the HFHS group (n=4), it was 43,384, yielding a p-value of 0.248. Similarly, no statistically significant variation in hyperplasia emerged from data obtained through imaging analysis and quantification between male and female rat cohorts. For males (n=4), adipocyte count was 56,689, while for females (n=4), it was 38,374, resulting in a p-value of 0.149. The assessment of cell hypertrophy in the IFP between the chow and HFHS diet groups (n=8) revealed a significant difference for cell areas <500 um^2 (p=0.021), signifying a higher count of adipocytes with reduced area in the chow diet group (Figure 1). Conversely, no statistically significant differences were observed within other area ranges (Figure 1; 500-999 um^2 to 3000-3499 um^2). The analysis of cell hypertrophy, assessed by cell area, among male and female rats (n=8), revealed significant differences within larger areas ranging between 1000-3499um² (p=0.021, p=0.021, p=0.020, p=0.020, and p=0.020, respectively). In contrast, no noteworthy distinctions in cell hypertrophy were evident for the smaller cell areas (Figure 1; <500um² and 500-999um²).

DISCUSSION: The relationship between diet, sex, and cellular inflammatory responses highlighted by these results holds significant implications for understanding the potential connection between obesity and metabolic OA. While hyperplasia in the IFP seemed unaffected in both diet groups and both sex groups, the results of our study indicate that a HFHS may have a more pronounced impact on certain cellular mechanisms related to hypertrophy in the IFP, which could be relevant to the development and progression of metabolic OA. The increased adipocyte size in the HFHS group and male cohort, as indicated by our results, may potentially lead to an increased secretion of inflammatory cytokines and adipokines, which play crucial roles in mediating the inflammatory response inside the joints. This heightened release of cytokines and adipokines could contribute to local inflammation, exacerbating the progression of metabolic OA. Consequently, understanding the relationship between hypertrophy, hyperplasia, and inflammation in the IFP is pivotal in unraveling the mechanisms regarding the pathogenesis of metabolic OA and developing strategies to mitigate its impact through targeted interventions. The most important limitation of our study is the relatively small sample size which might impact the generalizability of the findings.

SIGNIFICANCE/CLINICAL RELEVANCE: As osteoarthritis remains a prevalent and debilitating joint condition, the study's findings offer insights into how certain dietary patterns, particularly those high in fat and sugar, might impact cellular mechanisms within the infrapatellar fat pad (IFP), causing local systemic inflammation, leading to metabolic OA. Considering the differences observed between male and female cohorts, the study hints at potential sex-related variations in cell behavior, underlining the importance of accounting for sex-specific factors in understanding OA development.

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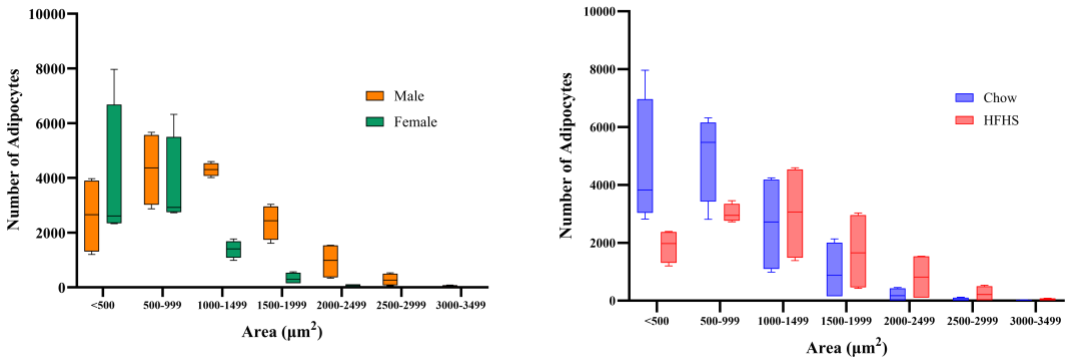

Figure 1: Evaluation of Cell Hypertrophy in the Infrapatellar Fat Pad (IFP) across Male vs. Female rats and Chow vs. HFHS Diet groups.