Title

Effect of weight cycling on progression of knee joint degenerative disease in overweight and obese individuals: 4-year mri data from the osteoarthritis initiative

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circadian running activity, triglyceride-related SF metabolite features, and serum factors. Although the reduced voluntary running activity of HF diet mice may contribute to some diet-related distinctions, the extensive network differences between CF and HF mice support the hypothesis that obesity broadly alters systemic and local metabolic pathways involved in joint tissue structure and OA pathology.

PRESENTATION NUMBER: 13
PAIN IN WOMEN WITH KNEE AND/OR HIP OSTEOARTHRITIS IS RELATED TO ADIPOSE TISSUE DYSFUNCTION - DATA FROM THE KHOALA COHORT

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Purpose: Beyond the link between metabolic diseases and osteoarthritis (OA) risk, some studies have suggested an association between metabolic syndrome or visceral obesity and OA-related pain. Here, we investigated whether biomarkers of adipose tissue dysfunction or of systemic inflammation could be associated with OA-related pain.
Methods: We cross-sectionally analyzed patients with knee and/or hip OA at inclusion in the 863 patients included in the national multicentric KHOALA cohort (NCT00481338). We used visual analogic scale (VAS) for pain, the Western Ontario and McMaster Universities Arthritis Index (WOMAC) and Osteoarthritis Knee and Hip Quality of Life (OAKHQOL) pain subscores. For WOMAC and VAS pain, higher scores reflect more symptoms, while it is the opposite for OAKHQOL. At inclusion, we measured in the serum ultra-sensitive C reactive protein (usCRP), reflecting systemic inflammation, leptin and total adiponectin for calculation of leptin:adiponectin ratio (LAR), a marker of adipose tissue dysfunction associated with central adiposity, high-molecular-weight adiponectin, visfatin and apolipoproteins (apoA1, apoB100). Univariate and multivariate analyses using stepwise linear regression models were performed to search for correlation between pain assessments and these biomarkers, with adjustment on age and Kellgren-Lawrence score and with stratification by sex.
Results: In 596 women with hip and/or knee OA, multivariate analyses indicated that higher pain intensity was associated with higher LAR (VAS pain: β=0.49; p=0.0001, OAKHQOL pain: β=-0.46; p=0.0002, WOMAC pain: β=0.3; p=0.002) in the whole group. Analyzing knee and hip OA populations separately, these correlations were found for both joints in multivariate analyses (knee OA: VAS pain $\beta = 0.55$ p = 0.0001; OAKHQOL pain: $\beta = -0.50$ p = 0.0002; WOMAC pain $\beta = 0.30$ p = 0.006; hip OA: VAS pain $\beta = 0.64$ p = 0.03; OAKHQOL pain: $\beta = -0.55$ p = 0.04). Pain intensity correlated also with usCRP level (VAS pain: β= 0.27; p=0.02, OAKHQOL pain: β =-0.31; p=0.01) and Kellgren-Lawrence score. Serum visfatin, high-molecular-weight adiponectin, Apo A1 and Apo B100 levels were not related to pain level, whatever the score used. In 267 men, no correlation between biomarkers and OA pain was found.
Conclusions: Serum LAR and usCRP level are associated with pain level, independently of radiographic structural severity in women with hip and/or knee OA, emphasizing the role of adipose tissue dysfunction and of systemic inflammation in pain experience in the OA female population.

PRESENTATION NUMBER: 14
EVIDENCE OF DIFFERENTIAL METABOTYPES IN SYNOVIAL FIBROBLASTS AND SYNOVIAL FLUID IN OBESE HIP OSTEOARTHRITIS PATIENTS

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Purpose: Purpose: Synovial inflammation (synovitis) is considered to be an active process in the development and progression of OA joint pathology. Synovitis occurs at the onset of OA and is thought to contribute to the degradation of articular cartilage via the release of pro-inflammatory cytokines from synovial fibroblasts, which can induce the expression and release of cartilage matrixmetalloproteases and aggrecanases that degrade type II collagen and proteoglycans respectively. Importantly, we recently reported that synovial fibroblasts from end-stage obese OA patients display an enhanced inflammatory phenotype, compared to normal-weight OA patients. Identifying the central molecular drivers of this enhanced inflammatory profile in obese OA patient synovial fibroblasts may help to identify therapeutic opportunities to modify the inflammatory OA synovial fibroblast phenotype thus reducing joint inflammation and slowing disease progression. Critically, there is now evidence from inflammatory fibrotic disorders and from rheumatoid arthritis that metabolic changes are associated with, and may mediate, the switch to an inflammatory activated synovial fibroblast phenotype. Therefore, the aim of this study was to determine whether synovial fibroblasts and synovial fluid from obese and normal-weight OA patients exhibit different metabolic metabotypes.
Methods: Synovial joint tissue and synovial fluid was obtained from n=9 hip OA patients, who were either of normal-weight or obese and were undergoing elective joint replacement surgery (Ethical approval NRES 16/SS/0172). Synovial fibroblasts were isolated and cultured from diced synovial tissue. Basal and TNF-α stimulated synovial fibroblast oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) was determined using a Seahorse XF Analyser. Lactate secretion was measured by Lactate Colorimetric Assay (Sigma-Aldrich, UK). The expression of lactate transporters and IL6 was determined by qPCR, and IL-6 secretion by ELISA. Synovial fluid metabolome was determined by 1H NMR and analysed using MetaboAnalyst v4.0.
Results: When challenged with TNFα, obese OA synovial fibroblasts exhibited increased ECAR (7.1 $\pm$ 0.7 vs 3.9 $\pm$ 0.8, p=0.04 n=3) and OCR (12.49 $\pm$ 1 vs 11.86 $\pm$ 0.7 n=5, p= 0.002), indicative of elevated glycolysis and increased basal respiration respectively, compared to similarly challenged normal-weight OA synovial fibroblasts. Furthermore, normal-weight synovial fibroblasts showed a concentration dependant increase in lactate secretion when challenged with TNFα. In contrast, obese OA synovial fibroblasts exhibited higher basal levels of lactate secretion and could not increase lactate secretion further when challenged with TNFα. Metabolomics analysis of synovial fluid from obese (n=8) and normal weight (n=8) hip OA patients using 1H NMR Spectroscopy revealed an increase in glucose-alanine cycle, serine and glycine metabolism as well as glutamine metabolism in obese OA synovial fluid samples (p= 0.06)
Conclusions: This is the first study to identify differences in the metabolic phenotype of OA synovial fibroblasts and OA synovial fluid between obese and normal-weight OA patients. Our findings demonstrate an intimate link between the inflammatory and metabolic profile of OA synovial fibroblasts and synovial fluid in OA patients and further confirm the effect of obesity on the synovial fibroblast phenotype. Targeting the metabolism of the obese OA synovial fibroblast may provide therapeutic opportunities to reduce the enhanced inflammation observed in OA patients with synovitis.

PRESENTATION NUMBER: 15
EFFECT OF WEIGHT CYCLING ON PROGRESSION OF KNEE JOINT DEGENERATIVE DISEASE IN OVERWEIGHT AND OBESE INDIVIDUALS: 4-YEAR MRI DATA FROM THE OSTEOARTHRITIS INITIATIVE

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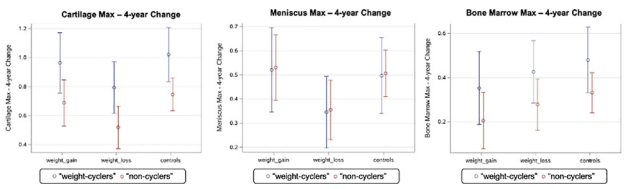
Purpose: Obesity is prevalent in approximately 39.8% of US adults (data from 2015/2016), and is a risk factor for cardiovascular disease, hypertension, type 2 diabetes, and osteoarthritis (OA). Weight loss is frequently recommended for obese and overweight individuals to reduce the risk of obesity-related diseases, and has shown protective effects. However, sustained weight loss is often difficult to maintain, and an estimated 20-30% of individuals attempting weight loss experience episodic variation in body weight. This repetitive pattern of weight loss and regain has been termed “weight cycling”. The purpose of this study is to investigate the associations between weight cycling and knee joint degeneration in overweight and obese individuals with different patterns of weight change over 4 years.

Methods: A sample of 2271 individuals from the Osteoarthritis Initiative Database was included in this study. BMI measurements were used to determine the annual rate of change in BMI over 4 years in each individual. The slope of the regression line was multiplied by 4 to determine overall magnitude of BMI change, and the percentage change over 4 years was defined as the magnitude of BMI change divided by the baseline BMI. In addition to the magnitude of weight change, the trajectory of weight change was analyzed as it may affect longitudinal changes in joint structure and clinical symptoms. We devised a method to classify individuals into those with "steady" and those with "cyclic" weight change based on the root mean square error (RMSE) of the regression line. We obtained RMSE measurements from each individual's regression model, and their weight fluctuation was determined based on the RMSE. We defined a subject with BMI variability, termed "weight-cycler" in this study, as an individual with an RMSE value in the top 10% of all RMSE values. The remaining 90% of individuals were termed "non-cyclers". In addition, individuals were classified into three groups based on their annual changes in BMI over 4 years: weight loss (>-5% change), weight gain (>5% change), and controls without weight change (-3 to 3% change). 3T MRI was used to quantify knee cartilage T2 (a measure of cartilage biochemical composition) and cartilage thickness annually over 4 years in all subjects. Whole-organ magnetic resonance imaging scores (WORMS) were obtained to semi-quantitatively assess cartilage, meniscus, and bone marrow abnormalities in 958 subjects at baseline and 4-year follow-up. The longitudinal differences in cartilage T2 and thickness between "weight-cyclers" and "non-cyclers" were assessed using general estimating equations, while the differences in WORMS outcomes were compared using general linear models. An interaction between cycler group and weight change group was included to determine if the relationship between weight cycling and knee joint outcomes was modified by weight change. All analyses were adjusted for age, sex, baseline BMI, and weight change category.

Results: Over 4 years, increases in maximum cartilage WORMS scores (coeff.$_{\text{("weight cyclers" vs. "non-cyclers")}}$=0.27, 95% CI=0.09-0.45, p=0.002) and bone marrow abnormalities (coeff.$_{\text{("weight cyclers" vs. "non-cyclers")}}$ = 0.14, 95% CI =0.006-0.28, p=0.04) were significantly greater in "weight-cyclers" vs. "non-cyclers" (Fig. 1). Longitudinal changes in meniscus scores were not significantly different (p = 0.89) between "weight-cyclers" and "non-cyclers". The interaction between weight cyclers group and weight change group was not-significant (p>0.05) in all analyses. Adjusting for weight cycling group (BMI variation), the weight loss group had significantly smaller changes in the maximum cartilage scores (coeff.=-0.22, 95% CI =-0.38 - -0.06, p=0.004) and maximum meniscus scores than controls (coeff.=-0.15, 95% CI =-0.28 - -0.01, p=0.02), while there were no significant differences in the weight gain group compared to controls (p>0.05). No significant differences in the rate of change of cartilage thickness or T2 values were found between "weight-cyclers" vs. "non-cyclers".

Conclusions: Overall, the Results of this study suggest that subjects with BMI variability/weight cycling have significantly greater degenerative changes in cartilage and bone marrow over four years compared to subjects that do not have high BMI variability, and the relationship is independent of the amount of weight change. These results suggest that weight cycling may exacerbate progression of degenerative changes of cartilage and bone marrow, regardless of the amount of overall weight change.

Figure 1: Changes in maximum WORMS scores (cartilage, meniscus, bone marrow) over 4 years in "weight-cyclers" with BMI variability vs. "non-cyclers" without BMI variability. Error bars represent 95% Confidence Intervals.



PRESENTATION NUMBER: 16

ASSOCIATIONS OF CENTRAL OBESITY WITH EARLIER ONSET OF OSTEOARTHRITIS SYMPTOMS

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Purpose: Obesity is a know risk factor for pain and osteoarthritis (OA), and in most studies, Body Mass Index (BMI) has been used to classify obesity (BMI>=30) in subjects at risk of OA and pain. However, BMI does not take into account the distribution of the fat mass. Waist circumference (WC) and waist to hip ratio (WHR) strongly correlates with abdominal obesity and are commonly used to measure the fat distribution and to determine central obesity. Central obesity is one of the most important components of metabolic syndrome and it has been demonstrated to be a stronger factor associated with knee pain, low back pain, and inflammation more than and, independent of BMI. In our population with knee and/or hip OA, we would like to determine whether central obesity is associated with an earlier presentation of joint pain and which joints are more affected by pain in subjects with OA and central obesity compared with subjects with OA without central obesity.

Methods: In this retrospective cohort study, we examined medical records and interviewed 770 patients with a confirmed diagnosis of OA, who attended the orthopedics outpatient clinic-referred from other services with advanced hip and/or knee joint wear and persistent joint pain. We asked the patients the age of onset of OA-pain in years and which joint was the first affected and which joints were currently affected by pain using the Numerical Rating Scale (NRS). Waist and hip circumferences were measured and central obesity was defined as unhealthy when the Waist to Hip Ratio (WHR) was equal or higher than 0.90 in men or equal or higher than 0.85 in women, according to the World Health Organization (WHO). Potential confounders in the relation central obesity and pain, like depression, anxiety, physical activity, education, alcohol intake, and smoking were analyzed. Analysis of variance (ANOVA), linear and logistic Regression Analyses was performed. Betas (β) and Odds Ratio (OR) with 95% confidence interval (CI) are presented. All analyses were adjusted for age, gender, and body mass index.

Results: In our population 25% of subjects were affected by hip-OA, 49% with knee-OA, and 26% with both joints affected. Knee was the first joint that reported pain in 56% of the subjects followed by hip (38%), low back (4%), and other joints (2%). From all 770 subjects included in the analysis, 46% were obese (BMI≥30). Most of our population (65%) had central obesity. BMI was slightly associated with earlier onset of OA-pain (B=-0.11, P= 0.07) and central obesity was significantly associated with earlier onset of OA-pain in years (B =-2.77, P = 0.002) and B = -2.53 P = 0.006, after adjustment for age, gender and BMI. Subjects with central obesity started with OA-symptoms 2.5 years earlier than subjects without central obesity (Fig. 1, P=0.006). The odds of starting with OA-pain before the age of 50 years in individuals with central obesity was 1.7 times higher compared with individuals without central obesity (OR: 1.72, CI: 1.07-2.78, P=0.025). In addition, our population with hip or knee OA reported low back pain (35.5%), hand (10%), shoulder (9.2%), foot or ankle pain (9.1%), or elbow pain (3.2%). Central obesity was associated with a higher number of joints affected by pain (Fig. 2). subjects with unhealthy central obesity had approximately 10.4% more joints affected by pain (Fig. 2, P= 0.04). Subjects with central obesity in addition to hip or knee OA-pain had higher odds of foot or ankle pain (OR=2.11, CI: 1.0-4.46) and low back pain (1.51, CI: 1.0-2.28).

Conclusions: BMI is a well-established risk factor for pain and OA and regarding joint pain central obesity is perhaps the most important obesity related-trait. Central obesity not only exerts influence on the number of joints with pain but might determine the age of onset of OA-symptoms. Subjects with central obesity and OA, are at higher odds of reporting low back and/or foot or ankle pain. Several potential mechanisms of the relationship between obesity and pain have been proposed. However, today we recognize that mechanical-structural explanations for the association of obesity with OA and pain are not the only ones. Metabolic-inflammatory factors associated with an excess of adipose tissue should be recognized as a more important factor for pain and pain initiation than BMI. According to our Results, central obesity