SAT0560

FROM A 2-YEAR MULTICENTRE CLINICAL TRIAL IN KNEE OSTEOARTHRITIS, A METABOLOMIC ANALYSIS REVEALS THAT OVER ACTIVATION OF THE CONVERSION PATHWAY OF PHOSPHATIDYLCHOLINE TO LYSPHOSPHATIDYLCHOLINE IS ASSOCIATED WITH KNEE CARTILAGE VOLUME LOSS OVER TIME

G. Zhai¹, J.-P. Pelletier², M. Liu¹, E. Randell³, J. Martel-Pelletier². ¹Discipline of Genetics, Memorial University of Newfoundland, St. John's, NL; ²University of Montreal Hospital Research Centre, Montreal; ³Department of Laboratory Medicine, Memorial University of Newfoundland, St. John's, NL, Canada

Background: While progression of osteoarthritis (OA) is variable, no tools yet exist to predict disease course.

Objectives: To identify, using a metabolomic approach, serum marker(s) for predicting knee cartilage volume loss over time measured by magnetic resonance imaging (MRI) in a 24 month Phase III clinical trial in patients with symptomatic knee OA.

Methods: 139 knee OA patients who completed the clinical trial according to protocol were selected from a 24 month DMOAD trial studying the effect of licofelone versus naproxen. MRI was performed at baseline and 24 months. Targeted metabolomic profiling was performed on serum collected at baseline. Metabolite ratios as proxies for enzymatic reaction were calculated and used in the analysis. The levels of 186 metabolites were measured and 152 met the quality control requirements. The metabolite concentrations were standardised using the Z-score. 21 952 pair wise metabolite ratios were analysed. A metabolome-wide significance level of $\alpha=2.3 \times 10^{-5}$ was defined after correcting multiple testing with the Bonferroni method. Univariable and multivariable analyses adjusted for age, sex, BMI and medication were performed. Gene expression analysis of human OA articular cartilage (n=32) and subchondral bone (n=39) tissues from total joint replacement, and controls (non-OA) from individuals having a fracture (n=21; n=9, respectively) was done to further explore the potential metabolic pathway(s).

Results: Data revealed that the baseline ratio of the metabolite lysophosphatidylcholine 18:2 (lysoPC 18:2) to phosphatidylcholine 44:3 (PC44:3) was associated with the cartilage volume loss in the lateral compartment (univariable, $b=-0.21 \pm 0.04$, $p=8.53 \times 10^{-7}$; multivariable, $b=-0.18 \pm 0.04$, $p=9.5 \times 10^{-6}$). Further experiments demonstrated that the lysoPC 18:2/PC44:3 ratio was also significantly ($r=0.31$, $p=0.0002$) correlated with an articular degradation marker, COMP. The data of the increased lysoPC 18:2 to PC44:3 ratio involve a conversion pathway of PC to lysoPC which is catalysed by a phospholipase A2 (PLA2), suggesting a higher activity of PLA2. Data demonstrated that in both human cartilage and subchondral bone tissues, a PLA2, PLA2 group 5 (PLA2G5), was markedly over-expressed in OA cartilage and subchondral bone compared to these non-OA tissues (445% and 158% increase, respectively, all $p<0.02$). Interestingly, in these tissues TNF- α was also upregulated ($p=0.007$; $p=0.06$, respectively), and positively correlated with PLA2G5 ($r=0.71$, $p=0.02$).

Conclusions: Our data suggest that the ratio of lysoPC 18:2/PC44:3 is predictive of greater risk of cartilage loss in OA. We speculate that this specific conversion pathway may produce a bioactive molecule like oleoylethanolamide (OEA), which has been demonstrated to bind to a novel cannabinoid receptor, GPR119, thus could be a novel therapeutic target for OA treatment.

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SAT0561

MITOCHONDRIAL BACKGROUND INFLUENCES THE JOINT EVOLUTION IN A CONPLASTIC MOUSE MODEL OF AGEING

I. Rego-Pérez¹, A.V. Lechuga-Vieco², M. Scotece¹, P. Filgueira-Fernández¹, S. Pértiga³, J.A. Enríquez², F.J. Blanco¹. ¹Servicio de Reumatología, INIBIC – HOSPITAL UNIVERSITARIO A CORUÑA, A Coruña; ²Grupo de Genética funcional del sistema de fosforilación oxidativa, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid; ³Unidad de Epidemiología Clínica y Bioestadística, Inibic – Hospital Universitario A Coruña, A Coruña, Spain

Background: Several studies showed interesting associations between mtDNA haplogroups and different OA-related features, including prevalence, incidence or progression of the disease¹⁻³. The use of conplastic animals-individuals with the same nuclear genome but different mtDNA variants-provides an accurate tool to study the influence of the mitochondrial background in the ageing process⁴.

Objectives: To study the influence of mtDNA variation in the degree of joint deterioration of the knees of aged animals using a conplastic mouse model of ageing

Methods: mtDNAs from C57BL/6 and NZB/OlaHsd mice were used. These mtDNAs differ by 12 missense mutations, 4 tRNAs mutations, 8rRNAs mutations and 10 non-coding region mutations. Then, a conplastic mice strain was developed with the C57BL/6 nuclear genome and the NZB/OlaHsd mtDNA (BL/6^{NZB}) to compare with the original C57BL/6 strain (BL/6^{C57}) in animals of 25 and 75 weeks. A total of 38 limbs from 19 mice were processed to perform histologic analyses: 8 BL/6^{NZB}25 w, 10 BL/6^{NZB}75 w, 10 BL/6^{C57}25 w and 10 BL/6^{C57}75 w.

Results: Mankin score data showed significantly increased values in all knees from both strains at 75 w compared with 25 w ($p<0.001$), confirming the ageing of the joint. When 75 w mice were selected (table 1), the BL/6^{C57} strain showed a significantly increased score in whole joint ($p=0.038$), femoral condyles ($p=0.021$) and medial femoral condyle ($p=0.015$) than BL/6^{NZB} strain. Safranin-O/Fast-green ratio value at 75 w was higher in the medial compartment of BL/6^{NZB} compared with BL/6^{C57} (both tibial plateau and femoral condyle); however, only the differences detected in the medial compartment of the tibial plateau reached the statistical significance ($p<0.001$), whilst the differences detected in the femoral condyle borderline the statistical significance ($p=0.091$).

The width of the epiphyseal plate was analysed in both tibia and femur bones. The results showed significantly decreased values in BL/6^{C57} at 75 w compared with the same strain at 25 w in tibial plateau ($p<0.001$) and femoral condyle ($p=0.049$); however, these differences were not observed in animals belonging to BL/6^{NZB} strain. In addition, the BL/6^{C57}75 w strain also showed significantly lower values in tibial plateau than BL/6^{NZB} strain at the same age ($p=0.032$).

Abstract SAT0561 – Table 1. Mankin score grading of cartilage destruction in conplastic mice BL/6^{C57} and BL/6^{NZB} at 75 w

	LTP	LFC	MTP	MFC	TP	FC	Med comp	Lat comp	Whole joint
BL/	5,80	4,40	4,67	6,00	10,44	10,37	10,14	10,20	19,71
6 C57	$\pm 1,81$	$\pm 1,07$	$\pm 2,06$	$\pm 1,07$	$\pm 3,43$	$\pm 1,85$	$\pm 3,02$	$\pm 2,39$	$\pm 4,57$
BL/	5,00	4,38	4,40	4,44	9,40	8,71	8,44	9,13	17,43
6 ^{NZB}	$\pm 2,11$	$\pm 0,92$	$\pm 2,12$	$\pm 1,24^*$	$\pm 1,78$	$\pm 1,70^*$	$\pm 2,60$	$\pm 1,55$	$\pm 1,72^*$

LTP: lateral tibial plateau; LFC: lateral femoral condyle; MTP: medial tibial plateau; MFC: medial femoral condyle; TP: tibial plateau; FC: femoral condyle; Med comp: medial compartment; Lat comp: lateral compartment; * $p<0.05$ with respect to BL/6^{C57}

Conclusions: This study demonstrates the functional impact of mtDNA variation in the process of joint deterioration associated to ageing, leading to consider the mtDNA as a potential therapeutic target in osteoarthritis associated to ageing

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SAT0562

HIP SHAPE PREDICTS KNEE OSTEOARTHRITIS OUTCOMES OVER A DECADE IN OLDER-ADULTS

I.P. Munugoda¹, H.G. Ahedi¹, R.M. Aspdren², K. Wills¹, S.E. Graves³, M. Lorimer⁴, F. Cicuttini⁵, J.S. Gregory², G. Jones¹, M.L. Callisaya¹, D. Aitken¹. ¹Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia; ²Aberdeen Centre for Arthritis and Musculoskeletal Health, Institute of Medical Sciences, University of Aberdeen, Aberdeen, UK; ³Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR); ⁴South Australian Health and Medical Research Institute (SAHMRI), Adelaide, South Australia; ⁵Department of Epidemiology and Preventive Medicine, Monash University Medical School, Melbourne, Victoria, Australia

Background: Various hip shapes may be important as a risk factor for development and progression of knee osteoarthritis, due to the biomechanical link between the two joints.

Objectives: This study aims to identify the relationship between hip morphology and structural and clinical osteoarthritis outcomes in the knee over 10.7 years, in older-adults.

Methods: 377 community-dwelling older-adults aged 50–80 years were studied. At baseline, dual-energy X-ray absorptiometry images of the left hip were obtained and hip shapes were described using mode scores from an 85-point statistical shape model. MRI scans were conducted at baseline and a mean follow-up of 10.7(SD:0.67) years later, to assess right knee tibial cartilage volume and bone-marrow lesions(BMLs). Knee pain was assessed using Western Ontario and McMaster Universities Osteoarthritis Index(WOMAC). Knee replacement(KR) data were obtained by data linkage to the Australian Orthopaedic Association National Joint Replacement Registry. Linear mixed-effects, log-binomial models

and survival analysis, were used to investigate associations between hip shape modes and change in cartilage volume, incident BMLs, worsening knee pain and left KR respectively. All models were adjusted for baseline age, sex, BMI, knee injury or surgery and hip radiographic osteoarthritis (ROA), while the KR model was additionally adjusted for WOMAC pain and knee ROA.

Results: Ten hip shape modes were identified, describing 78% of the total shape variance in descending order from mode 01 (31% variance) to mode 10 (1.82% variance). Hip shapes with a larger greater trochanter (mode 07) were associated with lower knee cartilage volume loss (Beta:2.14, 95% CI:0.07,4.21), while a shorter and narrower femoral neck shape (mode 09) was related to increased volume loss (Beta:-3.86, 95% CI:-6.16,-1.56). Increasingly non-spherical femoral head (mode 04) was associated with an increased risk of incident BMLs (RR:1.19, 95% CI:1.07,1.34). Those with a longer, wider femoral neck and a larger femoral head (mode 01) had an increased risk of worsening knee pain (RR:1.33, 95% CI:1.09,1.61), whereas those with a smooth curving upper femoral neck (mode 09) had a lower risk of worsening knee pain (RR:0.78, 95% CI:0.67,0.90). A larger greater trochanter and wider femoral neck shape (mode 08) was associated with an increased risk of KR (RR:1.73, 95% CI:1.18,2.52), while increasing acetabular coverage (mode 10) was associated with a lower risk of KR (RR:0.54, 95% CI:0.36,0.8).

Conclusions: Hip shape variations were associated with significant MRI-based and clinical outcomes in knee over 10.7 years, possibly due to biomechanical, lifestyle or other factors related to both joints. These results suggest that hip shape may play an important role in the onset and progression of knee osteoarthritis over time.

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SAT0563

IDENTIFICATION AND VALIDATION OF PHYSICAL ACTIVITY PHENOTYPES FOR KNEE OSTEOARTHRITIS: A POPULATION-BASED COHORT STUDY

I.P. Munugoda¹, F. Pan¹, K. Wills¹, F. Cicuttini², S.E. Graves³, M. Lorimer⁴, G. Jones¹, M.L. Callisaya¹, D. Aitken¹. ¹Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania; ²Department of Epidemiology and Preventive Medicine, Monash University Medical School, Melbourne, Victoria; ³Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR); ⁴South Australian Health and Medical Research Institute (SAHMRI), Adelaide, South Australia, Australia

Background: The identification of phenotypes to reduce heterogeneity of characteristics is important in understanding the development and progression of knee osteoarthritis.

Objectives: This study aimed to identify physical activity (PA) phenotypes and to investigate the association of these phenotypes with tibial cartilage volume, bone marrow lesions (BMLs) and knee replacements (KR) over 10.7 years.

Methods: 1046 community-dwelling older adults aged 50–80 years were studied. At baseline, PA was measured by pedometers (steps/day), knee pain was assessed using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and body mass index (BMI) was determined utilising objective weight and height measures. MRI scans were conducted at baseline and 10.7 years to assess tibial cartilage volume and BMLs. The incidence of KR was determined by data linkage to the Australian Orthopaedic Association National Joint Replacement Registry. Latent class analysis was used to determine 'PA phenotypes' based on PA, BMI and WOMAC pain at baseline. Linear mixed-effects models and log-binomial models were used to estimate the associations between the identified PA phenotypes with change in cartilage volume, incident BMLs, and KR surgery over 10.7 years. All models were adjusted for age, sex, and history of knee injury or surgery, while the KR model was additionally adjusted for the prevalence of knee radiographic osteoarthritis.

Results: Three PA phenotypes were identified: Class 1: Normal/overweight participants with low levels of PA and low pain (42%); Class 2: Obese participants with low levels of PA and high pain (26%); Class 3: Normal/overweight participants with high levels of PA and low pain (32%). Mean cartilage volume loss over 10.7 years was 465±231 mm³. 221 participants had an incident BML while 74 had an incident KR. Class 2 participants had greater cartilage volume loss over 10.7 years (Beta: -79.9, 95% CI -135.8,-23.9) and, had a higher risk of KR (RR 2.36, 95% CI 1.20, 4.67) compared to Class 1 participants. Class 3 was not associated with cartilage volume loss (Beta: -36.2, 95% CI -86.6, 14.1) or risk of KR (RR 0.86, 95% CI 0.40, 1.84) compared to Class 1. Similarly, PA phenotypes were not associated with incident BMLs (Class 2: RR 1.15, 95% CI 0.88, 1.50; Class 3: RR 1.19, 95% CI 0.93, 1.54; compared to Class 1).

Conclusions: Our findings support the existence of homogeneous PA profiles, and suggest that PA interacts with body weight and knee pain and has long-term impacts on osteoarthritis outcomes.

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SAT0564

EFFECTS OF EDUCATION AND INCOME ON PREVALENCE, INCIDENCE, AND PROGRESSION OF RADIOGRAPHIC KNEE OSTEOARTHRITIS: AN ANALYSIS OF THE OSTEOARTHRITIS INITIATIVE DATA

I. Shirinsky, V. Shirinsky. Research Institute Of Fundamental And Clinical Immunology, Novosibirsk, Russian Federation

Background: Low socioeconomic status (SES) is one of the strongest predictors of morbidity and mortality from many chronic diseases including cardiovascular diseases, obesity, and diabetes.¹ There is insufficient data regarding impact of SES on knee osteoarthritis (OA).

Objectives: To evaluate the associations between education, income levels and prevalence, incidence, and progression of radiographic knee OA

Methods: For the current analysis we used data from the publicly available Osteoarthritis Initiative (OAI) database. The education status of the participants was dichotomized into either low/moderate or high educational attainment. The income status was dichotomized using 50 K US threshold. A baseline sample was used to analyse the impact of SES on knee OA prevalence (prevalence sample). To evaluate the effects of SES on knee OA incidence and progression we analysed the samples of OAI participants with KL <2 at baseline (incidence sample) and OAI participants with JSN <3 at baseline (progression sample), respectively. We used logistic regression models to assess the association between SES and prevalence and incidence of radiographic knee OA (defined as KL2 and JSN or joint replacement), and disease progression (defined as increase in semiquantitative JSN or a new knee replacement). Generalised estimating equations (GEE) were used to adjust for the correlation between knees. The models were adjusted for multiple covariates including age, race, and body mass index.

Results: Prevalence, incidence, and progression samples consisted of 4371 participants (8741 knees), 2268 participants (4535 knees), and 3950 participants (4013 knees), respectively.

Higher education attainment and higher income were associated with decreased prevalence of the knee OA in the crude analyses. After adjustment for confounders these associations became insignificant (Table). There was no effect of SES on incidence and progression of the knee OA.

Table

	Prevalence			
	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Education	0.8 (0.7–0.9)	<0.001	1.05 (0.9–1.18)	0.48
Income	0.71 (0.64–0.8)	<0.001	1 (0.87–1.4)	0.97

OR – odds ratio, CI – confidence interval

Conclusions: Higher levels of education and income are linked with decreased prevalence of radiographic knee OA. Lack of this association after adjustment suggests confounding or mediating effects of other risk factors. Future studies are needed to delineate the precise mechanisms of how SES impact knee OA.

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SAT0565

ADJUSTING FOR THE INTRA-ARTICULAR PLACEBO EFFECT IN KNEE OSTEOARTHRITIS THERAPIES

I. Simsek¹, T. Phalen¹, A. Bedenbaugh¹, M. Phillips², J. Tambiah¹. ¹Samumed, LLC, San Diego, USA; ²McMaster University, Ontario, Canada

Background: Currently, there is a large debate regarding the appropriateness of intra-articular (IA)-saline injection as a "placebo" comparator in knee osteoarthritis (OA) trials and meta-analyses. There is substantial evidence to suggest that the injection of saline into the joint is not without treatment effect.

Objectives: This study aimed to assess the current literature's estimates of the IA-saline treatment effect against a range of appropriate minimal clinically important difference (MCID) values to identify if IA-saline provides a therapeutic effect that is not indicative of a null-effect.

Methods: The treatment effect estimates of IA-saline and topical placebo for knee OA pain, relative to oral placebo, were derived from a published network meta-analysis Bannuru et al, 2015 and compared across a range of plausible