14 TRANSCRIPTION FACTOR HES1 MODULATES OSTEOARTHRITIS DEVELOPMENT IN COOPERATION WITH CAMKII

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Purpose: We recently reported that the RBPj-dependent Notch signaling in chondrocytes modulates endochondral ossification and osteoarthritis (OA) development. Since this signal was shown to be mediated through induction of the target gene Hes1 in chondrocytes, the present study investigated the role of Hes1 and the underlying mechanism during OA development.

Methods: We generated tissue-specific knockout mice of Hes1 by mating Sox9-Cre knock-in mice or tamoxifen-inducible Col2a1-Cre transgenic mice (Col2a1-CreFL) with mice homozygous for a floxed Hes1 allele (Hes1FL). To analyze the role Hes1 in articular cartilage after maturation, we injected tamoxifen into 7-week-old Col2a1-CreFL/Hes1fl mice and created a surgically induced OA model by resecting the medial collateral ligament and the medial meniscus in the knee joints one week after the injection. The OA severity was quantified by the OARSI histopathology grade 8 weeks after the surgery. We examined transcriptional regulation by chromatin immunoprecipitation (ChIP) sequencing using human chondrogenic SW1353 cells transfected with the FLAG-tagged Hes1 construct, and confirmed the transcriptional activation by luciferase assay using HeLa cells transfected with the reporter construct containing a promoter fragment of the marker genes. For expression analyses, we performed immunofluorescence and realtime RT-PCR. For protein-protein interaction analyses, we performed co-immunoprecipitation (Co-IP) assay in SW1353 cells. For functional analyses, we used lentiviral doxycycline-inducible expression vectors in mouse chondrogenic ATDC5 cells and examined the expression of target genes by real-time RT-PCR.

Results: Although the Sox9-Cre/Hes1FL mice died in the perinatal period, the embryos exhibited normal skeletal growth. However, the OA development was prevented in the Col2a1-CreFL/Hes1fl mice. When both these proteins were lentivirally co-overexpressed in mouse chondrogenic Col2a1-CreFL cells, Hes1 expression was enhanced. When both these proteins were lentivirally co-overexpressed in mouse chondrogenic SW1353 cells, Hes1 expression was induced more highly than a single overexpression of each gene. Furthermore, a mutagenesis of Hes1 in the serine residue of CaMKII phosphorylation site caused a loss of its ability to induce Mmp13 and Adamts5.

Conclusions: Hes1 modulates OA development through the transcriptional regulation of Mmp13 and Adamts5 through the phosphorylation by CaMKII, Notch/Rbpj and Hes1 pathways in cooperation with OA.

15 RECEIVING OPERATING CHARACTERISTICS ANALYSIS OF OUTCOMES OF TOTAL JOINT REPLACEMENT FOR OSTEOARTHRITIS

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Purpose: Persistent pain after joint replacement is a considerable problem affecting between 7% and 20% of total knee replacement (TKR) patients and 2-8% of total hip replacement (THR) patients. The aim of the present study was to assess the factors that contribute to patient satisfaction and mobility post joint replacement.

Methods: 735 knee and hip osteoarthritis patients were recruited from orthopaedic clinics 1 year post total joint replacement and a research nurse assessed their level of mobility, satisfaction with their surgery, medical history, pain intensity, PainDETECT questionnaire scores, quality of life and quality of sleep. Catastrophizing and illness behavior were also available for a subset of patients.

Results: Among the 308 patients who had undergone THR, 98% were very satisfied of the outcome of their surgery, 94% reported a significant pain improvement and 83% an improvement in their ability to walk post THR. 3.9% had undergone a revision surgery. This compared to 75% satisfaction in the 383 post TKR cases. 3.1% of whom had a revision surgery, 85% reported a pain improvement and 72% an improvement in mobility. Among patients who had undergone both TKR and THR procedures satisfaction was 84%, 90% reported a substantial pain improvement even though the rate of revision surgery has much higher (13.6%) than among TKR only or THR only cases. The factors that contributed to lack of satisfaction post surgery in THR cases were the WOMAC pain score (OR=25 95% CI 1.05-1.48 per Likert scale unit p<0.012) younger age (OR=0.92 95% CI 0.86-0.99 per year p<0.018) and presence of revision surgery (OR=8.13 95% CI 1.4-46 p<0.018). Among post-TKR patients the strongest factors contributing to lack of satisfaction were the WOMAC pain score (OR=1.15 95% CI 1.06-1.24 per Likert scale unit), poor sleep (OR=1.25 95% CI 1.04-1.49 in a scale 0-10) and presence of possible neuropathic pain (as defined by the PainDETECT questionnaire) (OR=1.90 95% CI 1.03-3.49). Among patients with both TKR and THR procedures the only significant factor contributing to satisfaction was the WOMAC stiffness score (OR=3.39 95% CI 1.21-9.48 per Likert scale unit). An analysis in a subset of 163 post-TKR cases on which catastrophizing measures were available revealed that, although a high catastrophizing score is indeed associated with satisfaction, this association was entirely mediated by pain and dropped from the model after adjusting for WOMAC pain scores. Using a receiver operating characteristics (ROC) analysis we found that among TKR cases, age, sex and BMI provided useful information on patient satisfaction (area under the curve(AUC)=0.496). On the other hand the presence of possible neuropathic pain (NP) alone achieved an AUC=0.643 [95%CI 0.58 - 0.705] on patient satisfaction.
satisfaction which reached AUC = 0.743 [95% CI 0.691 - 0.795] when added to age, sex, BMI, WOMAC score and poor sleep quality (see Figure 1).

**Conclusions:** Our data confirm the strong difference in patient related outcomes for THR and TKR and highlight the importance of understanding the factors that contribute to neuropathic pain like symptoms and to pain in general post TKR.

16 LIFETIME RISK OF TOTAL HIP AND KNEE REPLACEMENT AND TEMPORAL TRENDS IN INCIDENCE BY HEALTH CARE SETTING, SOCIOECONOMIC STATUS AND GEOGRAPHIC LOCATION

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**Purpose:** Estimation of the lifetime risk of joint replacement surgery is an emerging field in musculoskeletal epidemiology. While global burden of disease data are valuable for understanding disease incidence and prevalence and the relative impact of a disease on patients’ lives (1), lifetime risk provides an alternative method of quantifying population disease burden and associated healthcare utilisation. (2) Gaining insight into population-wide fluctuations, which may be independent of disease burden, can be useful for budget priority setting and assessing the impact of policy changes on healthcare utilisation. These data may also support advocacy activities for policy and funding changes. Our primary aim was to investigate lifetime risk of total hip (THR) and total knee (TKR) replacement surgery. As changes in the lifetime risk of joint replacement over time could be mediated by environmental, health system or patient and clinician-level factors, we also sought to describe temporal trends in incidence by relevant factors which may impact utilisation of these procedures.

**Methods:** We analysed a population-based cohort of patients who received a primary THR or TKR in Victoria, Australia from 1999 to 2008. Hospital separations and life tables were used to estimate lifetime risk. Temporal changes in THR and TKR incidence were examined according to healthcare setting (public versus private), socio-economic status (SES) and geographic location (regional versus metropolitan).

**Results:** We identified 45,775 patients receiving a primary THR and 43,570 receiving a primary TKR over the time period. The lifetime risk by year for each procedure for a person aged 40–49 years is reported in Figure 1. There was a greater increase in the lifetime risk of TKR when compared to THR, particularly for females. We also identified an increasing number of both procedures in private hospitals (increase in THR of 0.14 per 1000 and TKR of 0.60 per 1000 over the time period), for people in middle socio-economic groups (increase in THR of 0.11 per 1000 and TKR of 0.07 per 1000), low socio-economic groups (increase in THR of 0.19 per 1000 and TKR of 0.10 per 1000) and in rural areas (increase in THR of 0.24 per 1000 and TKR of 0.70 per 1000) (Figure 2). The proportion of rural patients treated in private hospitals tended to be significantly less than patients in metropolitan settings (52.3% vs 68.6% for THR and 51.3% vs 65.7% for TKR, p<0.01 for both). With the exception of the increase in THRs in the middle socio-economic group, increases were more pronounced for TKRs over the time period.

**Conclusions:** The larger increase in lifetime risk of TKR over the study period could be partly attributed to the ageing population, with more people aged over 80 receiving TKRs, increased rates of sporting injuries(3) and rising rates of obesity (all risk factors for knee OA incidence (4,5,6,7)). As the number of TKRs increased most in private hospitals, it may also relate to insurance incentives introduced at the beginning of the study period. Increases in the number of joint replacement procedures performed for patients in regional areas suggest some reductions over time in known disparities. The larger increase in incidence for patients in regional areas could relate to greater previously unmet need, a higher burden of OA in rural areas related to higher rates of obesity and manual occupations and the increased provision of orthopaedic services in rural areas over the past decade. The lifetime risk of THR performed on women was found to be similar to males, despite a higher burden of hip OA. This difference may indicate under-utilisation of surgery by females. Similarly, low SES was associated with an overall lower incidence of THR and TKR during the study period. In Australia, people with low SES generally have reduced access to the private hospitals. This study confirms findings from England and Canada which have reported reduced utilisation of TKR by lower SES groups.(8-10) These disparities warrant further investigation.

**References**