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The Effect of Homocitrullinated Lipoproteins on Immune Cell Function in Rheumatoid Arthritis- Associated Cardiovascular Disease

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Objectives: Rheumatoid Arthritis (RA) patients who express antibodies to citrullinated proteins (ACPA) are at an increased risk of cardiovascular disease (CVD) compared to the general population. The mechanism by which ACPA contribute to CVD risk is unknown. Citrulline is structurally similar to homocitrulline and homocitrullinated low density lipoproteins (HcitLDL) have been identified in atherosclerotic plaque. A prior study showed that HcitLDL promotes the formation of lipid-laden macrophages (foam cells), which are implicated in the pathogenesis of atherosclerosis. We aim to determine whether HcitLDL affects immune cell function in Rheumatoid Arthritis.

Methods: Human LDL was homocitrullinated by incubating with potassium cyanate and confirmed by Western Blot. A mouse monocyte/ macrophage cell line (RAW 264.7) was treated with phorbol myristate acetate followed by treatment with HcitLDL, unmodified LDL and acetylated LDL (a known potent inducer of foam cells). Foam cells were determined by morphology using oil red O staining and phase-contrast microscopy. These experiments were replicated at least 7 times. To confirm results in primary cells, circulating human monocytes were isolated from healthy controls, treated with macrophage colony stimulating factor (M-CSF) to differentiate into macrophages and then treated with lipoproteins as above. Serum from RA patients and healthy controls were tested for antibodies to HcitLDL using an in-house enzyme-linked immunosorbent assay (ELISA) at least in triplicate. ACPA were determined using a commercial anti-cyclic citrullinated peptide 2 (anti-CCP2) assay (Euroimmun™). RA patients were recruited from the St. Joseph's Health Care rheumatology clinic (London, Ontario). Healthy controls were age and sex-matched.

Results: HcitLDL and acetylated LDL similarly induced foam cell production: median proportion of foam cells to macrophages of 0.89 (0.73-1.00) and 0.95 (0.56-1.00), respectively, which was significantly higher than unmodified LDL: 0.13 (0-0.44) and untreated macrophages: 0.08 (0-0.25); $p < 0.0001$. Study subjects were 68% female with a mean age of 55 (SD 13) years (N=29 RA and 31 control subjects). The majority of RA subjects (85%) were positive for ACPA; controls were negative for ACPA. RA subjects had higher levels of antibodies to HcitLDL than healthy controls: 16.0 (SD 22.4) RU/ml versus 8.1 (SD 7.8) RU/ml; $p = 0.0203$.

Conclusion: HcitLDL strongly promotes foam cell production in vitro and antibodies to HcitLDL were detected in RA subjects suggesting that HcitLDL affects immune cell function. Further studies are needed to determine whether HcitLDL contributes to the pathogenesis of RA-associated CVD.

2

Knee Pain Intensity is Associated with Muscle Adiposity in the Whole Thigh and Hamstrings of Women with Knee Osteoarthritis

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Objectives: Knee osteoarthritis (OA) is a degenerative disease associated with significant pain and disability. Ectopic fat volume in the thigh, including intramuscular fat (IntraMF; fat within a

muscle belly) and intermuscular fat (IMF; fat within the deep fascia and between muscles bellies), is associated with impaired physical performance in knee OA. However, the association between knee pain and the presence of thigh ectopic fat within and between muscles remains unknown. We investigated the relationship of thigh IntraMF, IMF and muscle adiposity with self-reported knee pain in individuals with knee OA.

Methods: Women (n=20) with radiographic, symptomatic knee OA had the thigh of their most symptomatic knee imaged using a Discovery MR750 3.0T magnetic resonance imaging (MRI) scanner (General Electric Healthcare, Milwaukee WI). The iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL) sequence obtained 60 fat-separated axial slices (3 mm slice thickness). Images were analyzed using SliceOmatic® software with region-growing to quantify IMF, IntraMF and lean muscle volumes (cm³) (Tomovision, Magog QC). Muscle adiposity was calculated as the percent of total muscle volume consisting of IntraMF for the whole thigh and individually for the quadriceps and hamstrings muscle groups. Normalized knee extensor strength (Nm/kg) was calculated as the mean of five isometric contractions using a Biodex System 2 dynamometer (Biodex, Shirley NY). Knee pain intensity was assessed using the self-reported Western Ontario and McMaster Universities Arthritis Index (WOMAC). Linear regression analyzed the relationship between muscle adiposity, IntraMF or IMF volume with knee pain, controlling for normalized knee extensor strength.

Results: Whole thigh muscle adiposity (B=-3.547; p=0.040), but not the volume of IntraMF (B=-0.204; p=0.072) or IMF (B=0.003; p=0.924), was directly related to WOMAC self-reported knee pain intensity. Furthermore, hamstrings (B=-2.402; p=0.036) but not quadriceps (B=-2.673; p=0.177) muscle adiposity was related to self-reported knee pain intensity.

Conclusion: Whole thigh muscle adiposity, and particularly hamstrings adiposity, was directly associated with knee pain intensity in women with knee OA. Thus, the percent of the hamstrings muscle comprised of IntraMF is related to knee pain intensity. This relationship persisted despite controlling for normalized knee extensor strength, an important predictor of pain in OA.

Individuals with greater thigh muscle adiposity experience more knee pain, which leads to a question for future research to explore the relationship between IntraMF and physical disability in women with OA.

3

Autophagy Can Regulate the Unfolded Protein Response and Affect Pathogenesis of Ankylosing Spondylitis

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Objectives: Ankylosing spondylitis (AS) is a chronic inflammatory and disabling arthritis predominantly affecting the spine. The pathogenesis of AS is not well understood. HLA-B27 misfolding, endoplasmic reticulum (ER) stress and the unfolded protein response (UPR) have been proposed as potential pathogenic factors. We have recently reported increased expression of autophagy markers and MHC-I free heavy chains (FHC) but no UPR in the gut of AS patients. Autophagy may protect cells from UPR. The aim of this study was to assess the impact of autophagy on expression of FHC and UPR. The studies were done in vitro and in the gut of AS patients.

Methods: The in vitro system consisted of antigen presenting cells with low endogenous

expression of MHC-I and stably transfected with HLA-B27. This is an excellent system to study the changes related to HLA-B27 without the interference of other MCH-I molecules. We used C1R-B27 cells which are B-lymphoblastoid cells stably expressing HLA-B27. These cells were investigated by fluorescence microscopy and electron microscopy for presence of autophagy. Autophagy was inhibited in these cells using 3-Methyl Adenine (3-MA). Autophagy and UPR was measured by gene expression and FHC level assessed by flow cytometry. As autophagy activation was initially reported in the gut, we tested the impact of autophagy suppression on UPR in lamina propria mononuclear cells (LPMC) isolated from gut of 10 AS patients.

Results: Autophagosome formation and active autophagy modulation was demonstrated in C1R-B27 cells by fluorescence and electron microscopy. Six-hours following the use of 3-MA, there was 60% Inhibition of autophagy in C1R-B27 cells as assessed by decreased expression of ATG16L1 and HSP8. Following autophagy inhibition there was a significant increase (7-fold) in XBP1 splicing and the expression of BiP, CHOP and PERK reflecting increase in UPR. Contemporaneously FHC expression increased following autophagy inhibition. Inhibition of autophagy in LPMCs showed similar results with increased FHC expression and activation of UPR.

Conclusion: Autophagy can mask UPR and could be a protective response in a pro-inflammatory milieu. Down-regulation of autophagy can increase both FHC accumulation and UPR. Perturbations in the fine balance between UPR and autophagy could be pathogenic in AS.

4

Comparison of Systemic Lupus Erythematosus in 3 Different Asian Ethnic Groups: Results from the 1000 Canadian Faces of Lupus Cohort

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Objectives: Systemic lupus erythematosus (SLE) is more prevalent and severe in non-Caucasians including Asians. However, Asian ethnicity includes cultural, geographic and genetic diversity. There is limited data examining SLE among North American Asian ethnicities. We describe SLE in 3 Asian subgroups from a large SLE cohort.

Methods: The 1000 Faces of Lupus is a multicentre Canadian cohort of over 2000 patients. Sociodemographics, ACR classification criteria (ACRc), autoantibodies, disease activity scores (SLEDAI), Systemic Lupus International Collaborating Clinics damage index (SDI) scores, and treatments are collected using standardized tools. Ethnicity was self-reported. Asian subgroups were divided by origin country into East Asian (EA), Southeast Asian (SEA), South Asian (SA) and Central Asian (CA). Baseline data for Asians and Caucasians were abstracted and cross-sectional univariate analyses including t-tests, one-way ANOVA, and chi-square tests were

performed.

Results: There were 334 Asians (EA=176, SEA=78, SA=78, CA=2), and 1275 Caucasians. CA were excluded. Asian onset age was similarly young (EA=23±13 years; SEA=21±10 years; SA=20±11 years) compared to Caucasians (33±15 years, p<0.001). Childhood onset was frequent in Asians (EA=49%; SEA=51%; SA=61%) compared to Caucasians (17%, p<0.001). Over 40% of Asians were immigrants. More Asians were males (EA=15%; SEA=16%; SA=19%) compared to Caucasians (10%, p=0.008). Over 90% of Asians completed high school compared to Caucasians (83%, p=0.007). Most Asians had the highest income tier (EA=55%; SEA=42%; SA=58%), similar to Caucasians (51%). ACRc and SLEDAI scores were not different. All Asians had more nephritis (EA=57%; SEA=63%; SA=51%) compared to Caucasians (33%, p<0.001). More Asians were dsDNA+ (ever) (EA=62%; SEA=63%; SA=78%) compared to Caucasians (52%, p<0.001). More SEA were antiSm+ and antiRNP+ (ever) (EA=31%; SEA=50%; SA=30%; p=0.01, and EA=20%; SEA=32%; SA=22%; p=0.03), but all Asians were higher than Caucasians (19%, p<0.001; 16%, p<0.001). More SA were antiphospholipid positive (ever) (EA=26%; SEA=18%; SA=37%, p=0.04) but overall similar to Caucasians (24%). Treatment with prednisone (EA=55%; SEA=67%; SA=65%), cyclophosphamide (EA=13%; SEA=21%; SA=20%), and mycophenolate (EA=15%; SEA=19%; SA=9%) was relatively frequent in Asians. Mean disease duration in Asians was 8 years but most had no damage (SDI=0, EA=66%; SEA=64%; SA=79%) compared to Caucasians (47%, p<0.001).

Conclusion: This is the first study to compare SLE in North American Asian subgroups. Childhood onset is more common and disease appears severe but not different between Asians. Young onset age and a high proportion of first generation immigrants suggest the potential for a growing burden of SLE in this population. Future studies of outcomes and optimal treatments are indicated.

5

Fecal Incontinence and Association with Bowel Dysfunction in Systemic Sclerosis: A Canadian Multicenter Study

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Objectives: Fecal incontinence (FI) is a complication of systemic sclerosis (SSc), but its exact epidemiology and optimal management remain unknown. The purpose of this study was to establish the prevalence and severity of FI in an SSc cohort, to study the association between FI and constipation, small intestinal bacterial overgrowth (SIBO) and other potential predictors of FI, and to determine the impact of FI on health-related quality of life (HRQoL) in SSc.

Methods: We performed a multicenter, cross-sectional study of 271 patients with SSc followed in the Canadian Scleroderma Research Group registry (CSRG). In addition to the standardized

data collection protocol, participants were asked to complete three validated questionnaires: Bristol stool scale (BSS; measuring consistency of stool from 1, being hardest, to 7, being completely liquid stool), Jorge Wexner score (JWS; FI severity score ranging from 0-20, with 20 being most severe), and Fecal Incontinence Quality of Life scale (FIQOL; measuring 4 domains: lifestyle, coping/behaviour, depression/self-perception, embarrassment). The Rome III criteria were used to define constipation. Descriptive statistics and multivariate regression analyses were generated to determine associations between the JWS and other clinical variables.

Results: Mean age was 59.3±12.1 years, 87.4% were women, median (interquartile range, IQR) disease duration was 10.3(6.6-17.8) years and 30.0% had diffuse cutaneous SSc. Median BSS was 4.0(3.0-4.0), 103(39.6%) subjects met the criteria for constipation and 34(13.2%) received antibiotics for SIBO since disease onset. FI, defined as a JWS≥5, was identified in 74(27.3%) subjects; among them 33(12.2%) were mild (score 5-9) and 41(15.1%) moderate to severe (score≥10). In multivariate logistic regression analyses, variables associated with FI were(OR(95% confidence interval)): loose(BSS≥6) vs well-formed(3≤BSS<6) stools(5.93(1.81-19.42), p=0.003); history of forceps use(2.37(1.13-4.94),p=0.022); constipation(3.21 (1.46-7.06),p=0.004) and history of antibiotic use for SIBO(4.82(1.88-12.32),p=0.001). Other variables associated with FI in univariate but not multivariate analyses included advancing age (p=0.031), female gender (p=0.002), urinary incontinence (p<0.001), use of stool softeners (p=0.022) and domperidone (p=0.034). No difference was found with disease duration (p=0.918), limited or diffuse cutaneous disease subsets (p=0.670) or SSc-specific antibodies (all p>0.4). HRQoL decreased significantly as severity of FI increased (correlation coefficients of JWS with all 4 domains of FIQOL between -0.6 and -0.7, all p<0.001).

Conclusion: In this multicenter study, FI was common and often severe in SSc. Loose stools, SIBO, as well as constipation were strongly associated with FI. FI had a strong negative impact on HRQoL. These data can inform the design of future interventional studies aimed at improving the management of FI and HRQoL in SSc.

6

Risk of Diabetes Mellitus in Rheumatoid Arthritis Associated with Medications Used in RA: A Population Based Cohort Study

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Objectives: Previous research reports an increased risk of Diabetes Mellitus (DM) in RA compared to non-RA individuals. Our objective was to evaluate the effect of the medications used in RA on the risk of DM.

Methods: We conducted a population-based cohort study of all incident RA cases in British Columbia, identified between 1996 and 2006, followed until 2010, using administrative health data. Individuals were selected as RA cases based on a previously validated criteria. DM was defined using the previously validated National Diabetes Surveillance System definition, i.e. two physician visit within one year or one hospitalization with a diagnostic code for diabetes (ICD-9 code 250.X, ICD-10 code E11.X), with the additional requirement of at least one diabetes medication (oral hypoglycemic or insulin) dispensed. Individuals with DM prior to index date were excluded. A Cox proportional hazards model evaluated the risk of DM associated with

current use of: glucocorticosteroids (GC), OH-chloroquine, anti-TNF, methotrexate (MTX), and NSAIDs, evaluated as time-dependent variables, after adjusting for age, gender, markers of disease severity available in administrative data (prior orthopedic surgery, ever seeing a rheumatologist, rate of RA related visits), Romano comorbidity index, and comorbidities potentially related to DM measured at baseline.

Results: The sample included 26,166 RA cases (67% female; mean [SD] age 57.6[17.2] years), contributing 175,935 person-years of follow-up. Diabetes occurred in 1,416 cases, yielding an incidence rate of 8.01 per 1,000 patient-years. GC and NSAID use were associated with an increased risk of DM [aHR (95%CI):1.96 (1.71-2.25); and 1.20 (1.07-1.35), respectively]; and OH-chloroquine, anti-TNF, and MTX, with a decreased risk of DM [aHR (95%CI): 0.59 (0.49-0.71); 0.68 (0.44-1.04); and 0.71 (0.59-0.84), respectively].

Conclusion: We observed that glucocorticosteroid use was associated with a two-fold increase in risk of DM, and OH-chloroquine with a reduced risk of DM, consistent with their known effects on glucose metabolism. While MTX and anti-TNF use were associated with a lower risk of DM, suggesting that controlling inflammation with DMARDs may reduce the risk of DM in RA. The association with NSAID use may be due to NSAIDs serving as a marker of active inflammation.

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Histopathology of Childhood Small Vessel CNS Vasculitis

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Objectives: Childhood primary small vessel CNS vasculitis (SVcPACNS) is an increasingly recognized inflammatory brain disease with high morbidity and mortality mandating an elective brain biopsy to confirm the diagnosis. The aim of the study was to systematically review biopsies of SVcPACNS patients and inflammatory and epilepsy controls and to determine characteristic features defining the diagnosis of SVcPACNS.

Methods: A previously developed, standardized brain biopsy review instrument was applied to consecutive full thickness brain biopsies of pediatric cases and controls collected at a single center. Standardized stains including Hematoxyllin & Eosin, histochemistry of immune cell subsets plus electron microscopy. Nine North American expert neuropathologists were blinded reviewed to the patient's presentation, diagnosis and therapy. All biopsies were de-identified and scored independently by two reviewers. Univariate analyses compared variable between groups; correspondence analysis determined the multi-dimensional relationship of histological variables and patient diagnoses.

Results: A total of 31 brain biopsy specimens of children with SVcPACNS, 12 with epilepsy and 11 with non-vasculitic inflammatory brain disease controls were included. Correspondence analyses revealed distinct clusters of the three diagnoses based on dimensions of location of infiltrate and subtype/ severity of inflammation. Significant histological characteristics found to set apart SVcPACNS from controls included angiocentric ($p<0.01$) and/or perivascular infiltrates ($p=0.04$), evidence of endothelial cell activation ($p<0.01$) and inflammation in both grey and white matter ($p<0.01$). The infiltrate was found to be primarily T-cell mediated (CD3+ 86%, CD8+ 90%) only 27% of SVcPACNS biopsies had evidence of B cells. Features reported in

adult PACNS including granulomas, necrosis or fibrin deposits were absent in all biopsies. Leptomeningeal inflammation was non-diagnostic.

Conclusion: Distinct histological features were identified on brain biopsies of SVcPACNS and may help defining the disease. These were absent in biopsies of children with epilepsy and non-vasculitic inflammatory brain diseases and allow for the development of diagnostic criteria.

8

Biologic Therapy Treatment Complications in the Alberta Aboriginal Population with Rheumatoid Arthritis

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Objectives: Aboriginal people with rheumatoid arthritis (RA) have more severe disease and an increased number of comorbid conditions, which may result in higher rates of adverse events when using biologic therapy.

Methods: The Alberta Biologics Pharmacosurveillance Program (ABioPharm) is a longitudinal RA cohort study, linked to population-based administrative databases (physician claims and hospitalizations). We calculated incidence rate ratios (IRR) for adverse events comparing Aboriginal to non-Aboriginal groups, including all-cause hospitalization, serious infections, malignancy (lung, breast, colorectal, lymphoproliferative), cardiovascular events (myocardial infarction, congestive heart failure, cerebrovascular disease), thromboembolic events and death, using Poisson regression to adjust for age at biologic start, low socioeconomic status, urban vs rural residence, comorbidities (Deyo-Charlson), number of rheumatologist visits, history of joint replacement surgery, extra-articular features, baseline DAS28, baseline HAQ, number of previous DMARDs, steroids at baseline visit, and standardized for age and sex.

Results: The cohort includes 1,545 patients (n=83 Aboriginal) with a total of 8,145 person-years of follow-up. Aboriginals were younger at initiation of the first biologic (50 vs 55 years), with more comorbidities, higher baseline DAS28ESR scores (mean 6.11 vs 5.19) and slower rates of improvement for tender and swollen joint counts in the first year of treatment. Aboriginal patients had a higher risk of all-cause hospitalization (IRR 1.4, 95%CI 1.1 to 1.8, p=0.01), malignancy (IRR 2.6, 95%CI 1.1 to 5.7, p=0.02) and thromboembolic events (IRR 2.7, 95%CI 1.7 to 4.2, p<0.001). They also had higher risk of serious infections (IRR 3.2, 95%CI 2.5 to 4.0, p<0.001), with significantly more episodes of skin and soft tissue infections (IRR 3.8, 95%CI 1.5 to 9.6), osteomyelitis (IRR 6.6, 95%CI 1.8 to 25.1) and pyelonephritis (IRR 8.4, 95%CI 2.0 to 35.3). Aboriginal patients were similar to non-Aboriginal patients in the risk for cardiovascular events (IRR 0.7, 95%CI 0.5 to 1.1, p=0.03). The mortality rate was 0.7 per 100 person-years in the non-Aboriginal group, with no deaths in the Aboriginal group.

Conclusion: Aboriginal patients experience higher rates of all-cause hospitalization, serious infections, malignancy and thromboembolic events, but not cardiovascular events, during treatment with biologic therapy. These findings are important to inform treatment decisions to initiate biologic therapy in Aboriginal patients, and the need for frequent monitoring during therapy.

9

Understanding Erosions Inside-Out: Erosion Depth Predicts Bone Repair over 2 Years in Rheumatoid Arthritis

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Objectives: Building evidence suggests that erosion repair occurs in RA, particularly in well controlled disease. Moreover, erosive intrusion into the bone marrow may provide access to cellular and molecular factors that promote healing. Our objective was to determine if baseline erosion depth is predictive of erosion repair in disease-controlled RA patients over 2 years.

Methods: From a single rheumatology clinic, 22 RA patients concurrently taking DMARD or biologic therapy underwent bilateral MRI of the hands at baseline and 2 year follow-up. Using both coronal and axial images, a single reader measured the maximum depth and width of metacarpal head erosions identified on EERA software. Erosions were grouped into quartiles for baseline depth and width. Image evaluation was repeated after 72h for 6 patients, and the smallest detectable change (SDC) for both depth and width were determined. Using SDCs as thresholds, erosions were categorized as regressing (repairing) or non-regressing (no change or progressing) in both the depth and width dimensions. Fisher`s exact test and odds ratios with 95% confidence intervals were used to determine whether baseline erosion depth or width predicts changes in depth or width.

Results: Patients were 91% female with mean (SD) age 55.9 (9.3) years, DAS28 4.8 (1.5), and symptom duration 4.8 (5.3) years. Forty-nine metacarpal head erosions were identified, with a mean (SD) depth of 4.3 (1.5) mm, 2 year depth change of 0.26 (1.20) mm, width of 4.6 (2.1) mm, and 2 year width change of -0.07 (1.24) mm. Depth SDC was 0.62 mm with 8 regressors identified, and width SDC was 1.15 mm with 5 regressors identified. Baseline depth was predictive of change in depth ($p < 0.001$), with 4th quartile OR = 50.40 (5.08–500.00), and 7 of the 8 depth regressors ranking the 4th quartile of baseline depth. Baseline depth was not predictive of change in width ($p = 0.584$), with 4th quartile OR = 2.27 (0.33–15.51). Baseline width was not predictive of change in depth ($p=0.640$), 4th quartile OR = 1.03 (0.18–5.96), or change in width ($p=0.087$), 4th quartile OR = 5.83 (0.844–40.32).

Conclusion: In disease-controlled RA patients, reduction in erosion depth, ostensibly originating from repair at the base of the erosion, was significantly more probable in deeper, though not necessarily wider erosions. Changes in erosion width were not predicted by baseline depth or width. Identification of efficacious therapies may allow for modest erosive repair in RA patients with deeper erosions.

10

Impact of MRI on Diagnostic Reclassification in Axial Spondyloarthritis: Data from the Screening for Axial Spondyloarthritis in Psoriasis, Iritis, and Colitis Study (SASPIC)

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Objectives: Although MRI is the most sensitive imaging modality for early diagnosis of axial spondyloarthritis (axSpA) it is costly and not readily available across Canada. It is unclear to what degree MRI assessment influences diagnostic ascertainment of axSpA in routine practice. We aimed to assess the impact of MRI evaluation on diagnostic reclassification of axial SpA in unselected patients presenting with undiagnosed back pain to rheumatology practice.

Methods: The Screening for Axial Spondyloarthritis in Psoriasis, Iritis, and Colitis (SASPIC) Study is aimed at the development and validation of a triage strategy for detection of axial SpA in patients presenting with undiagnosed back pain. Consecutive patients <46 years of age with ≥ 3 months undiagnosed back pain with any one of psoriasis, acute anterior uveitis, or colitis diagnosed by the relevant specialist undergo routine clinical evaluation by a rheumatologist for axial SpA. The rheumatologist determines the presence or absence of axial SpA and the degree of confidence in the diagnosis (-10 to +10 on numerical rating scale) after the clinical evaluation, again after the results of labs (B27, CRP) and radiography, and then again after the results of MRI evaluation. Radiographs and MRI scans are also assessed centrally for diagnosis of axial SpA. We assessed the degree of diagnostic reclassification after each step descriptively at the categorical level (axial SpA yes/no) and also according to the degree of confidence (mean (SD) change towards definite SpA or definitely not SpA).

Results: To date 106 patients (45.3% male, mean age 34.1 years, mean back pain duration 7.0 years, B27+ 31.1%) have been referred with iritis (24.5%), psoriasis (11.3%), colitis (64.2%). A diagnosis of axSpA was made in 62.3% and 56.8% of patients before and after review of the labs and radiography, respectively. Radiographic sacroiliitis according to modified New York criteria (mNY) was reported in 57% according to site reads but in only 15% according to central read. MRI evaluation was conducted in 39 patients (43.6% mNY negative). After review of the MRI scan diagnosis of axSpA decreased to 38.5%, 8 (21%) being reclassified from SpA to non-SpA and 1(3%) from non-SpA to SpA. When SpA was diagnosed, confidence in the diagnosis increased by mean of 0.47 (2.97); conversely, when non-SpA was diagnosed confidence increased by mean of 3.25 (3.17).

Conclusion: MRI evaluation results in disease reclassification more frequently than labs and radiography. There is substantial discrepancy in radiographic interpretation of sacroiliitis.

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CHRNA7 Genetic Variants are Associated with Radiographic Severity and Progression in Ankylosing Spondylitis (AS)

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Objectives: Clinical studies have repeatedly demonstrated that smoking is associated with ankylosis in AS. The objective of this study was to determine if an interaction exists between genetic variants known to be associated with the nicotine metabolism pathway, smoking status and ankylosis in AS.

Methods: 76 AS patients from University of Toronto cohort, satisfying the modified New York criteria were studied. Patients were assessed with a standardized protocol which included serial radiographic assessments. Genotyping was performed using the Sequenom MassARRAY system

(iPLEX GOLD). Forty-one SNPs were chosen from three genes related to smoking metabolism (CHRNA7, UGT2B10 and UGT2B17). Uninformative SNPs and those failing Hardy-Weinberg equilibrium (HWE) were removed from analysis. Multiple linear regression analysis was performed controlling for age, gender and smoking habit. An interaction term between smoking and each SNP was introduced into the multiple linear regression models to examine the association among smokers and non-smokers, respectively.

Results: Of the 76 AS patients, 40% were smokers, and 78% were male. 35 patients exhibited disease progression (msasss score >0) and the mean radiographic progression was 0.99 mSASSS ss unit/yr. After filtering, 16 SNPs were used for the regression analyses. For radiographic severity, two SNPs from CHRNA7 gene were associated with initial msasss scores [(rs11071593, dominant model $p=0.0005$; genotype $p=0.001$) and [rs7178176, dominant model $p=0.0005$; genotype $p=0.001$]. For radiographic progression, two additional SNPs from CHRNA7 gene were associated msasss progression [(rs2337506, recessive model $p<0.001$; genotype $p=0.0003$)] and [rs12910885, recessive model $p<0.0001$; genotype 0.0001)]. Regarding interaction with smoking and genetic variants and radiographic severity, only one interaction was significant: SNP rs61750900 from the UGT2B10 gene among smokers had significantly lower msasss scores than non-smokers ($p=0.0084$).

Conclusion: We have demonstrated a significant association between SNPs in CHRNA7 gene and AS radiographic severity and progression. Interestingly, CHRNA7 is not only important in the nicotine metabolism pathway but is also required for acetylcholine inhibition of macrophage TNF- α release. Interaction with smoking, genetic variants related to nicotine metabolism and ankylosis is not clearly demonstrated. This may be due to the small number of patients studied and so further validation is required with an independent cohort.

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Cognitive Impairment in Lupus Patients: Identification of the Best Screening Test and Assessment for Associated Factors

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Objectives: There is an unmet need for a cognitive function screening test that can be administered to patients with SLE in clinic. The objectives were to determine: 1) prevalence of Cognitive Impairment (CI) in SLE, 2) validity of Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) as screening tests of CI in SLE against external constructs (Hopkins Verbal Learning Test-Revised (HVLT-R), Controlled Oral Word Association Test (COWAT)) and 3) associated factors with CI.

Methods: Consecutive patients followed at a single centre between Feb 2014 and June 2015 were recruited. HVLT-R, COWAT, MoCA and MMSE were administered.

Sensitivity/specificity, positive (PPV)/negative (NPV) predictive values and positive likelihood ratio (LR+) of MoCA and MMSE were determined. Patient-reported outcomes included questionnaires on intellectual ability (Reynolds Intellectual Screening Test (RIST)), anxiety (Beck Anxiety Inventory (BAI)), depression (Centre of Epidemiologic Studies Depression Scale (CES-D)) and social support (Medical Outcomes Study Social Support Survey (MOS-SSS)). Regression analyses determined associations with CI.

Results: Of 98 patients, 48% had CI using MoCA and 38% using HVLT-R. Sensitivity was higher for MoCA (68%) compared to MMSE (24%), though MMSE was more specific (90%)

than MoCA (64%). PPV and LR+ were similar in MoCA and MMSE (PPV: 53%, 60%; LR+: 1.9, 2.5, respectively), but NPV was higher in MoCA (77%) than MMSE (66%). Univariate Analyses: CI patients had higher CES-D scores (i.e. more depressive symptoms) (OR 1.05, 95% CI: 1.01-1.09, $p=0.01$) and an absence of antiphospholipid antibodies (OR 0.36, 95% CI: 0.14-0.92, $p=0.03$) than those without CI. This did not hold in multivariate analysis. There were no significant differences in sex, ethnicity, age at assessment visit, age at SLE disease diagnosis, steroid treatment, cardiovascular events, hypertension, diabetes, dyslipidemia, smoking status, SLEDAI-2K score, RIST (intelligence score), BAI (anxiety), or MOS-SSS (social support) score in patients with and without CI. Multivariate Analyses: Shorter SLE disease duration from diagnosis (OR 0.94, 95% CI: 0.90-0.98, $p=0.008$) and lower education (OR 0.81, 95% CI: 0.66-0.98, $p=0.03$) were significantly associated with CI in multivariate analysis. Each one-year of SLE follow-up reduces the probability of CI by 6%. Each one-year increase in education decreases the chance of developing CI by 17%.

Conclusion: CI is highly prevalent (47%) using MoCA. Considerations of cost/administrative burden and psychometric properties make MoCA the preferential screening test for CI in SLE. Shorter SLE disease duration from diagnosis increases risk while higher education protects against CI.

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Reliability Analysis of Two Short Medication Adherence Questionnaires in Patients with Rheumatoid Arthritis

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Objectives: Adherence to disease modifying anti-rheumatic drug (DMARD) therapy is suboptimal in patients with rheumatoid arthritis (RA). Efficient, low-cost measures are required for optimal monitoring of medication adherence in the rheumatology clinic. Self-report tools are the most efficient and cost-effective measures available. Recently, a 5-item version of the Compliance Questionnaire Rheumatology (CQR5) was developed from the original 19-item version to reduce patient burden. Reliability of the CQR5 over time has not yet been evaluated. Therefore, in a sample of RA patients, we evaluated reliability of the CQR5 against that of the 9-item Medication Adherence Report Scale (MARS9), another short medication adherence tool that was recently shown to be reliable in a sample of RA patients.

Methods: RA patients (disease duration ≥ 1 year) taking at least one DMARD prescription were randomly selected from a rheumatology outpatient clinic database. Patients were assessed at baseline and two weeks. Demographic data were collected at baseline. At each visit, medication adherence was assessed with the CQR5 and MARS9. Each item on the CQR5 was scored on a four point Likert scale (1 = strongly disagree, 4 = strongly agree). Scores for each item were then summed into a total score which varied between 5 and 20. For the MARS9, each item was scored on a five point Likert scale (1=always, 5 = never) and item scores were summed into a total score ranging from 9 to 45. On both questionnaires, higher scores indicated greater adherence. Reliability analysis was performed with the intraclass correlation coefficient (ICC) and the mean difference between measurements obtained at baseline and two weeks.

Results: 100 RA patients, [mean (SD) = 60.75(12.67) years], were recruited. 4 patients dropped out, therefore 96 were included in the analysis. In this sample, the CQR5 and MARS9 demonstrated excellent and fair to good test-retest reliability, respectively [ICCCQR5 =

0.78(CI95% = 0.69-0.85), $p < 0.01$; ICCMARS9 = 0.57(CI95% = 0.42-0.69), $p < 0.01$]. The differences in measurement between baseline and two weeks for the CQR5 [mean (SD) = -0.13(1.40)] and MARS9 [mean (SD) = -0.20(4.32)] were not significantly different ($p > 0.05$). However, the CQR5 had a lower and less variable mean difference than the MARS9, indicating greater consistency across measurements for this instrument.

Conclusion: We demonstrated that the CQR5 is a more reliable measure of medication adherence than the MARS9 in RA patients when it is used in a rheumatology clinic setting. A more in-depth investigation of the CQR5, including its validation against a gold standard, is currently underway. Supported by a CIORA grant.

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Determining the Minimal Clinically Important Difference for Systemic Lupus Erythematosus Disease Activity Index-2000 Responder Index-50 (S2K RI-50)

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Objectives: S2K RI-50 is a reliable and valid index able to measure $\geq 50\%$ improvement in disease activity. We aimed to determine the Minimal Clinically Important Difference (MCID) for S2K RI-50 in the Toronto Lupus Cohort (TLC).

Methods: Methods Analysis was conducted on patients seen between 2010-2012. The data retrieval form of S2K RI-50 was completed at each visit. Physician global assessment was determined at baseline visit on a visual analogue scale (0-10) and at follow up visits on a 7-point Likert scale (LS) (1-3 reflects worsening, 4 unchanged, 5 slightly improved, 6 moderate improved ($\geq 50\%$) and 7 much improved). This analysis is focused on the first follow up visit. Patients were collapsed into 2 groups based on LS; LS 6-7 and LS 5. The change of SLEDAI-2K was calculated between baseline and follow up SLEDAI-2K; the change of S2K RI-50 was calculated between baseline SLEDAI-2K and follow up S2K RI-50. MCID was determined based on 2 approaches: Anchor-based approach: We modeled the 1st follow up LS ≥ 6 as the outcome variable, and continuous S2K RI-50 change as the predictor in Logistic Regression model. Area Under Curve was obtained to determine the predictive power of S2K RI-50. We also derived the best S2K RI-50 cut-off based on optimal sensitivity/specificity in ROC analysis. Distribution-based approach: Standardized Response Mean (SRM) was used to confirm the effect size. The Standard Error of Measurement (SEM) was derived based on the following equation: $SEM = \text{Pooled SDBaseline} \times \text{square root of } (1 - \text{test / retest reliability coefficient})$ (S2K RI-50 Test-retest reliability = 0.98 based on a previous publication from TLC).

Results: 509 patients were studied (age and lupus duration at baseline visit were 44.3 ± 14.7 and 15.2 ± 11.0 years respectively). 48 patients had an improvement of LS 6 or 7. The baseline SLEDAI-2K was 7.3 ± 4.8 . At follow up, SLEDAI-2K and S2K RI-50 change were 2.6 ± 4.2 and 4.2 ± 4.2 respectively. 34 patients slightly improved. Anchor-based approach: MCID is equal to 1.1 based on the ROC analysis (AUC 0.74, Sensitivity 62% and specificity 75%). Distribution-based approach: SRM of S2K RI-50 for LS 6-7 is -0.97 (95% CI: -1.3, -0.6) which is considered a large effect size. SEM is equal to 0.96 from the previous equation.

Conclusion: SRM confirmed that the effect size of S2K RI-50 is large. The estimated MCID of S2K RI-50 derived from both ROC analysis and SEM confirmed that it is close to 1.