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Association of adipokines with severity of knee osteoarthritis assessed clinically and on magnetic resonance imaging

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ABSTRACT

Objectives: We aimed to evaluate the association between the adipokines: Leptin, Adiponectin, Resistin, and high sensitive-C-reactive protein (hs-CRP) with clinical, radiographical and magnetic resonance imaging (MRI) assessment of knee osteoarthritis (OA) severity.

Design: We performed a cross-sectional study in participants with earlier knee OA. Demographics, clinical (WOMAC), radiographical and MRI (BLOKS scoring) severity of knee OA were assessed. Serum leptin, adiponectin, resistin and hs-CRP were measured. Association of adipokines and hs-CRP with clinical, radiographic and MRI severity outcomes were evaluated using regression models with adjustment with age, sex, and body mass index (BMI).

Results: 137 participants with earlier knee OA (82% women, mean ± SD age: 55.5 ± 7.8 years) were included. Participants had moderate knee OA symptoms, mean WOMAC pain and function were 30.6 ± 18.0, and 31.7 ± 19.8 respectively. Mean BMI was 27.0 ± 5.9 kg/m^2. After adjustment with age, sex and BMI, serum leptin was positively associated with osteophyte size, cartilage integrity, infrapatellar synovitis and effusion. While hs-CRP was associated with meniscus extrusion and adiponectin was associated with WOMAC pain and function.

Conclusion: Serum adipokines, particularly leptin was associated with severity of various structural defects of the knee joint on MRI beyond age, sex and BMI in earlier knee OA.

1. Introduction

Knee osteoarthritis (OA) is a prevalent chronic joint disease affecting over 250 million people with a rising disease burden around the world [1]. The etiologies of knee OA are multifactorial, classically relating with genetic and mechanical factors, with an inflammatory component becoming increasingly recognized [2]. These factors contribute to the damage and subsequent failure of repair of cartilage of the affected joint.

Obesity has been an established risk factor for the development of knee OA, with overloading of knee joints being an obvious cause of wear and tear on articular cartilage [3,4]. Adipose tissue secretes a variety of adipokines such as leptin, adiponectin and resistin. It has been hypothesized that adipokines secreted by the adipose tissue, could have a role in the pathogenesis of knee OA, providing a non-mechanical link between obesity and knee OA [5]. Adipokines create a low grade systemic inflammatory state that could contribute to the pathological changes associated with knee OA [6]. Leptin has a role in promoting satiety, reducing food intake, and controlling body weight. Yet, obese individuals have been shown to have high levels of circulating leptin and being insensitive to exogenous leptin [7]. Leptin has also been shown to modulate cartilage metabolism, with higher levels in synovial fluid among knee OA patients undergoing knee replacement surgery compared to controls without knee OA who undergone arthroscopy [8]. Adiponectin is one of the most abundantly secreted adipokine in circulation and has been previously shown to exert anti-inflammatory effects by reducing the production of proinflammatory cytokines [9–11]. Serum

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resistin was found to be elevated in knee OA patients as compared to healthy controls [12]. Synovial fluid resistin was shown to correlate with cartilage degradation markers MMP-1 and MMP-3, and hypothesized to have a direct effect on cartilage degradation [13]. Obesity induces a low grade systemic inflammation with an elevation in C-reactive protein (CRP), that has been reported to be elevated in knee OA patients compared to those without knee OA [14,15].

However, the role of adipokines in knee OA pathogenesis is still unclear with some studies suggesting leptin and adiponectin are associated with markers of cartilage degradation, and induce pro-inflammatory cytokines production from articular cartilage [16,17]. In contrary to this, adiponectin has also been shown to exert a protective effect on the progression of knee OA, inhibiting interleukin (IL)-1β induced Matrix metallopeptidase-13 (MMP-13) expression [18].

Severity of knee OA has been traditionally assessed using radiography showing bone features such as joint space narrowing, osteophyte formation, subchondral sclerosis, and joint erosion. However, these signs would only present later in the disease process. Magnetic resonance imaging (MRI) is an imaging method that can evaluate structures beyond the bone. In addition to bony features such as osteophyte size, MRI can assess cartilage thickness or loss, bone marrow lesions (BMLs), synovitis, joint effusion, and meniscus extrusion; all of which are characterized in early knee OA that cannot be detected using radiography [19]. Using MRI as an imaging modality would aid in the earlier diagnosis of knee OA.

Current literature evaluating the associations between adipokines, and knee OA has largely been focused on radiographic assessment of knee OA, data on the relationship between adipokines and MRI features is scarce. Thus, in this study we aim to investigate the association between the adipokines: leptin, adiponectin, resistin, and high sensitivity (hs)-CRP with MRI, radiographical and clinical assessment of severity in patients with knee OA.

2. Methods

2.1. Study design

We used the baseline data collected from a cross sectional study of 137 participants with persistent knee pain [20]. Clinical data, knee radiographic, MRI data, and biological samples were available. The study protocol was read and approved by the SingHealth Centralized Institutional Review Board (Ref: 2012/837/E), and informed consent was obtained from each participant prior to study.

We recruited participants aged 40–79 years old from the community through advertisements on social media. Secondary referrals were taken from primary healthcare centers (SingHealth polyclinics), and tertiary centers of Orthopedics and Rheumatology and Immunology departments at the Singapore General hospital, yet no referrals were received. Interested participants were invited to contact the study team via a telephone hotline and were subsequently invited to a screening visit if they had experienced persistent pain in at least one knee, on most days during the past month. The participants were examined by a rheumatologist (YYL) at the clinic. Patients who fulfilled the American College of Rheumatology clinical classification for knee OA were included [21]. We excluded diagnoses other than knee OA (e.g rheumatoid arthritis, spondyloarthritis, Paget's disease, hyperparathyroidism, hyperthyroidism, hypothyroidism) and significant joint injuries in the past one year. In addition, we excluded participants with advanced stage of knee OA (Kellgren and Lawrence (KL) grade 4 on radiography taken at baseline) and isolated patellofemoral knee OA. We also excluded participants with contraindications to MRI, such as renal impairment, pregnancy, claustrophobia, and bleeding tendency or receiving warfarin therapy that precludes aspiration of knee joints.

2.2. Clinical data collection

Age, sex, ethnicity, comorbidities (hypertension, hyperlipidemia, diabetes mellitus and coronary artery disease) and current medications were collected. The index knee was designated as the more symptomatic knee or the dominant knee if symptoms were similar. Body weight and height were measured in clinic to calculate the body mass index (BMI) in kg/m^2. Participants self-reported their clinical severity of knee OA using the Western Ontario and McMaster Universities Osteoarthritis index (WOMAC) [22]. The WOMAC index consists of 24 items, aggregates to three subscales: pain, stiffness, and physical function. Each subscale is standardized to obtain a score from 0 to 100, with higher scores indicating greater severity.

2.3. Radiographic assessment

All participants underwent posteroanterior fixed-flexion weight bearing radiography on both knees with a SynaFlexer lower limb positioning frame at recruitment. The radiography was taken by starting with a 10 ° caudal beam angle until achieving alignment of the anterior and posterior margins of the tibial plateau to within 1.2 mm target [23]. The radiographs were scored according to KL grading (0–4) of the tibiofemoral (TF) compartment by an experienced musculoskeletal radiologist (SBW) who was blinded to the condition of the participants. Scores from both knees were combined to give a KL Sum Score (0–8) [24]. A combined radiographic sum scoring of both knees is hypothesized to better represent the total burden of knee OA and should have higher relevant association with biomarkers measured systemically than scores taken from one knee. 70 radiographs (140 knees) from this study were re-rescored for KL grades by the original assessors, blinded to the original scores 8–12 weeks apart. The intraclass correlation coefficients (ICCs) of KL grade of TF compartment was 0.75 (95% confidence interval, CI: 0.60–0.84).

2.4. Magnetic resonance imaging assessment

All 137 participants had an MRI on their index knees within 2 weeks from recruitment. The MRI protocol and sequences were previously published [25,26]. In brief, the MRI was acquired in a 3 T S Skyra (2012, Simens, Erlangen, Munich, Germany) with the index knee immobilized in a 15 Channel Transmit Receive Knee coil. Intravenous contrast, Dotarem, 0.5 mmol/ml (Gadoteric Acid, Guerbet, France) was used with a maximum administered volume of 10 ml. The MRI features were evaluated according to the Boston Leeds Osteoarthritis Knee Score (BLOKS) scoring system [27]. All scoring was performed on non-contrast images. Under the BLOKS scoring, the following features were scored in several anatomical subregions, including osteophytes size (OST) (12 subregions), cartilage integrity (9 subregions), bone marrow lesion (BML) size (9 subregions), effusion size (one score for the entire knee), infrapatellar synovitis (one region), and meniscal extrusion (4 subregions). For each feature in each subregion, a score ranging from 0 to 3 was given with a higher score indicating higher severity [27]. We tabulated the MRI scores for each feature with summation of the number of subregions affected with severity score $\geq$1: OST size (0-12), percentage with full thickness cartilage loss (% Cart Full Thickness Loss) (0–9), BML size (0–9) and meniscal extrusions (0–4). Effusion size (one score for entire knee) and infrapatella synovitis (one region) were read as 0–3. All MRI were scored by an experienced musculoskeletal radiologist (JRT) who was blinded to the participant's clinical details. 20 (14.6%) MRI were read twice by the same assessor 8–12 weeks apart to derive the intraclass correlation coefficients (ICC) (One-way Random model). The first readings of MRI scores were used in this study. The ICC (95% confidence intervals, CI) for OST size (0.99, 95% CI: 0.96–0.99), BML (0.91, 95% CI: 0.77–0.97), and meniscal extrusion (0.91, 95% CI: 0.78–0.96) were excellent. The ICC for % Cart Full Thickness Loss (0.75, 95% CI: 0.47–0.89) and infrapatella synovitis (0.76, 95% CI: 0.48–0.90) were good. The ICC for effusion size (0.61, 95% CI: 0.20–0.83) was moderate.

2.5. Biological sample collection

We standardized blood collection from participants at recruitment with minimally 2 h post prandial. The collected samples were centrifuged

at 3000 rpm for 15 min, and serum was aliquoted to store at −80 °C until analysis.

2.6. Adipokine assessment

Serum (s) adipokines: leptin, adiponectin, and resistin were measured with commercially available enzyme-linked immunosorbent assay (ELISA) kits as per manufacturers' guidelines. We used the Milliplex Human Adipocyte Magnetic Panel Analytes (HADCYMAG-61K) manufactured by Merck. We also measured hs-CRP, a biomarker of systemic inflammation. All samples were measured in duplicates to obtain intra-assay coefficient of variations (CVs). The intra and inter-assay CVs of the kit standards were within 15% limits (Supplementary Table I).

2.7. Statistical analysis

The three (s) adipokines, leptin, adiponectin, and resistin, and hs-CRP were logarithmic transformed to achieve normal distribution. We evaluate Spearman's correlations between adipokines and hs-CRP. We constructed generalized linear model to assess the associations between each individual adipokines, hs-CRP and outcomes (MRI features, KL sum score and WOMAC pain and function). For associations between adipokines and outcome with p values of <0.2, we further explored the association with adjustment for age, sex BMI as the major risk factors for knee OA. In this pilot study, we did not evaluate adipokines in multivariable analyses.

For consistency of results, we conducted a sensitivity analysis limited to participants with radiographic KL $\geq$ 2. p values of $<$ 0.05 were considered statistically significant. All analysis were performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA).

3. Results

3.1. Baseline characteristics of participants

The baseline demographic and characteristics are described in Table 1. The mean (standard deviation, SD) age and BMI of the 137 participants (82% women) were 55.5 ± 7.8 years and 26.0 ± 5.9 kg/m^2 respectively. While all patients fulfilled the ACR clinical classification for knee OA [21], 53 (38.7%) had KL grade ≥2 on radiography of the index knee.

To further characterize this cohort, we evaluated their MRI features according to Luyten's criteria for minimal degenerative changes (at least 2 from: cartilage morphology grade 3–6, BLOKS cartilage grade 2 and 3, meniscus grade 3 and BML grade 2 and 3) post hoc [26]. Of the remaining 84 participants who had radiographic KL 0–1 in the index knee, 33 met minimal degenerative features on MRI described by Luyten and colleagues [28]. In short, 85 (62.0%) of the participants had fulfilled imaging evidence of knee OA, either KL $\geq$ 2 or minimal degenerative changes on MRI.

Patients in this cohort had moderate symptoms, WOMAC pain and function were 30.6 ± 18.0 and 31.7 ± 19.8, respectively. Participants had high prevalence of co-morbidities, most common being hypertension (30.3%), hyperlipidemia (38.7%) and diabetes mellitus (8.5%). 19.4% were obese with BMI ≥30 kg/m^2.

Correlations between adipokines and hs-CRP are shown in Supplementary Table II. No significant associations were noted between adipokines, except a mild correlation between leptin and hs-CRP (r = 0.33, p < 0.001).

3.2. Associations between adipokines and MRI features and other outcomes

Univariable analyses between adipokines and knee OA severity are summarised in Table 2. In particular, (s) leptin was significantly positively associated with, OST size, cartilage integrity, BML size, infrapatellar synovitis, effusion size, and meniscal extrusion. (s) Adiponectin was significantly associated with WOMAC function. (s) Resistin was not significantly associated with any of the tested outcomes. (s) hs-CRP was significantly positively associated with OST size, meniscus extrusion and KL sum score (Table 2). Leptin and hs-CRP were associated with KL sum score.

Table 1
Baseline characteristics of study participants (n = 137).

Age, years[a]	55.5 ± 7.8
Female, n (%)	112 (81.8)
BMI, kg/m^2[a]	26.0 ± 5.9
BMI ≥30 kg/m^2 (%)	27 (19.7)
Ethnicity, n (%)	
Chinese	111 (81.0)
Malay	14 (10.2)
Indian	10 (7.3)
Others	2 (1.5)
Comorbidities, n (%)	
Hypertension	41 (30.1)
Hyperlipidaemia	52 (38.0)
Diabetes mellitus	11 (8.1)
Coronary artery disease	4 (2.9)
Duration of knee pain, years[a]	5.1 ± 5.5
Fulfilled ACR Clinical Criteria for knee OA (%)	100
KL grading ≥ 2 or had minimal degenerative changes on MRI (%)	62.0
KL grade of index knee of TF compartment, n (%)	
0	40 (29.2)
1	44 (32.1)
2	35 (25.5)
3	18 (13.1)
KL grading ≥ 2, n (%)	53 (38.7)
MRI scoring of index knee [a]	
OST Size (0-12)	4.7 ± 4.3
% Cart Full Thickness Loss (0–9)	2.0 ± 1.7
BML Size (0–9)	2.6 ± 1.6
Infrapatellar Synovitis (0–3)	0.8 ± 0.9
Effusion size (0–3)	0.9 ± 0.8
Meniscus Extrusion (0–4)	0.5 ± 0.8
WOMAC pain (0–100) [a]	30.6 ± 18.0
WOMAC function (0–100) [a]	31.7 ± 19.8
Adipokines [a]	
(s) Leptin (ng/mL)	14.9 ± 16.4
(s) Adiponectin (μg/mL)	16.2 ± 20.9
(s) Resistin (ng/mL)	31.3 ± 42.4
(s) hs-CRP (mg/L)	3.6 ± 4.2

ACR, American College of Rheumatology; BMI, body mass index; BML, bone marrow lesion, hs-CRP, high sensitivity C-Reactive protein; KL grade, Kellgren and Lawrence grading; OA, osteoarthritis; OST, osteophyte; mg/L, milligrams per litre; μg/mL, micrograms per millilitre; Ng/mL, nanograms per millilitre; MRI, magnetic resonance imaging, (s), serum; TF, tibiofemoral; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; %, percentage.
[a] Mean ± SD.

3.3. Associations between adipokines and MRI features and other outcomes with adjustment for age, sex, BMI

After adjustment for age, sex and BMI, (s) leptin remained statistically significantly associated with OST size, cartilage integrity, infrapatellar synovitis and effusion size. The associations of (s) leptin with BML size and meniscus extrusion associations were attenuated after adjustment (Table 3). (s) Adiponectin was statistically significantly associated with WOMAC pain and function after adjustment, however, the association with MRI features was attenuated. Borderline association between adiponectin and WOMAC pain was only revealed after age, sex and BMI adjustment. (s) hs-CRP continued to be statistically associated with meniscus extrusion after adjustment. None of the adipokines or hs-CRP were associated with KL sum scores after adjustment of age, sex and BMI.

Results of sensitivity analysis limited to participants with KL ≥ 2 (n = 53) were generally consistent, although the statistical significance were attenuated due to small sample size (Supplementary Table III).

Table 2
Univariable analysis of association of adipokines and hs-CRP with MRI and other features.

Dependent Variable	β (95% confidence intervals), p-values			
	(s) Leptin	(s) Adiponectin	(s) Resistin	(s) hs-CRP
OST Size	**1.71 (1.07, 2.36), p < 0.001**	−2.07 (−3.96, −0.18), p = 0.032	−0.97 (−3.0, 1.10), p = 0.360	**2.34 (1.02, 3.66), p = 0.001**
% Cart Full Thickness Loss	**0.56 (0.31, 0.82), p < 0.001**	−0.56 (−1.29, 0.18), p = 0.138	−0.45 (−1.25, 0.35), P = 0.266	0.39 (−0.14, 0.91), p = 0.148
BML Size	**0.37 (0.12, 0.62), p = 0.004**	−0.17 (−0.87, 0.53), p = 0.631	−0.05 (−0.80, 0.71), p = 0.904	0.19 (−0.31, 0.69), p = 0.465
Infrapatellar Synovitis	**0.25 (0.10, 0.40), p = 0.001**	−0.16 (−0.57, 0.26), p = 0.452	−0.23 (−0.68, 0.22), p = 0.316	0.24 (−0.06, 0.53), p = 0.113
Effusion size	**0.26 (0.13, 0.39), p < 0.001**	−0.26 (−0.63, 0.11), p = 0.171	0.03 (−0.37, 0.43), p = 0.875	0.22 (−0.05, 0.48), p = 0.104
Meniscus Extrusion	**0.16 (0.03, 0.28), p = 0.012**	−0.17 (−0.51, 0.17), p = 0.314	0.07 (−0.30, 0.44), p = 0.708	**0.47 (0.34, 0.70), p < 0.001**
KL Sum Score	**0.42 (0.12, 0.73), p = 0.007**	−0.15 (−1.00, 0.70), p = 0.723	−0.17 (−1.07, 0.73), p = 0.712	**0.64 (0.05, 1.24), p = 0.035**
WOMAC Pain	2.17 (−0.73, 5.07), p = 0.143	7.65 (−0.18, 15.48), p = 0.055	−1.33 (−9.73, 7.07), p = 0.756	−0.40 (−6.07, 5.27), p = 0.891
WOMAC Function	1.82 (−1.39, 5.02), p = 0.266	**12.47 (4.01, 20.93), p = 0.004**	2.14 (−7.09, 11.36), p = 0.650	0.36 (−0.59, 6.62), p = 0.910

Bold, statistically significant associations.
BML, Bone Marrow Lesion; Cart, Cartilage; hs-CRP, high sensitivity C-Reactive protein KL Sum Score, KL, Kellgren and Lawrence grading; MRI, Magnetic Resonance Imaging; OST, Osteophyte; (s), serum; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table 3
Association of adipokines and hs-CRP with MRI and other features, adjusted with age, gender and BMI.

Dependent Variable	Adjusted β (95% confidence intervals)			
	(s) Leptin	(s) Adiponectin	(s) Resistin	(s) hs-CRP
OST Size	**1.08 (0.44, 1.71), p = 0.001**	−1.68 (−3.35, −0.00), p = 0.050	**–**	1.00 (−0.28, 2.28), p = 0.125
% Cart Full Thickness Loss	**0.37 (0.12, 0.63), p = 0.005**	−0.36 (−1.04, 0.32), p = 0.295	–	−0.02 (−0.54, 0.50), p = 0.930
BML Size	0.24 (−0.02, 0.50), p = 0.069	–	–	–
Infrapatellar synovitis	**0.23 (0.07, 0.39), p = 0.005**	–	–	0.16 (−0.16, 0.48), p = 0.332
Effusion size	**0.20 (0.06, 0.33), p = 0.005**	−0.18 (−0.54, 0.18), p = 0.327	−0.06 (−0.46, 0.33), p = 0.748	0.08 (−0.19, 0.35), p = 0.565
Meniscus Extrusion	0.01 (−0.11, 0.12), p = 0.884	–	–	**0.26 (0.04, 0.47), p = 0.022**
KL Sum Score	0.17 (−0.14, 0.47), p = 0.283	–	–	0.12 (−0.48, 0.72), p = 0.696
WOMAC Pain	1.51 (−1.60, 4.62), p = 0.340	**8.03 (0.125, 15.93), p = 0.046**	–	−2.79 (−8.88, 3.30), p = 0.369
WOMAC Function	–	**14.0 (5.77, 22.24), p = 0.001**	–	–

Bold, statistically significant.
BML, Bone Marrow Lesion; Cart, Cartilage; hs-CRP, high sensitivity C-Reactive protein KL Sum Score, KL, Kellgren and Lawrence grading; MRI, Magnetic Resonance Imaging; OST, Osteophyte; (s), serum; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

4. Discussion

In this cohort of earlier stage of knee OA, we demonstrated that (s) leptin was positively associated with osteophyte size, cartilage integrity, infrapatellar synovitis and effusion size amongst other MRI features after adjusting for major confounders namely age, sex, and BMI. (s) hs-CRP was associated with meniscus extrusion and adiponectin was statistically significantly associated with WOMAC pain and function.

(s) Leptin was shown to be associated with knee OA in several studies [29–31]. Data from a large population-based study with 6804 participants has shown a positive association between (s) leptin with a diagnosis of knee OA after adjustment for age, sex, ethnicity, and education [31]. However, severity was not graded in this study [31] and thus the association between leptin and knee OA severity cannot be elucidated. Staikos et al. have shown a positive association between (s) leptin and radiographic severity after adjustment for sex and BMI [30]. Kim et al. demonstrated a positive association between (s) leptin with both WOMAC scores and the length of medial osteophytes in 34 knee OA participants with swollen knees, after adjusting for age and BMI [29]. Zheng et al. evaluated the associations between adipokines and MRI in 179 patients with early knee OA and found that (s) leptin was not associated with knee OA severity. However, Zheng et al. demonstrated a positive associations between (s) leptin with patellar and tibial cartilage volume as shown on MRI, but not with (s) adiponectin and (s) resistin [32]. Our study concurs with existing literature that (s) leptin has a positive relationship with the severity of knee OA on MRI. This positive association was seen after adjustment for BMI, and thus suggests that leptin may play a role in the pathogenesis of knee OA beyond obesity [33]. The positive association between (s) leptin was beyond cartilage loss, but involves the inflammatory component, namely effusion and synovitis, which often precede cartilage loss [34].

The role of (s) adiponectin in knee OA severity has not been consistent. A few studies showed a negative association between (s) adiponectin and radiographic severity [32,35,36], while others showed null or positive associations [17,37,38]. Zheng et al. demonstrated that (s) adiponectin was significantly associated with reduced knee OA severity based on KL gradings after adjustment for age, sex and BMI [32], but had no significant association with knee cartilage volume on MRI [32]. Similarly, Wang et al. showed a negative correlation between (s) adiponectin and KL grading. They also showed a positive correlation between (s) adiponectin with infrapatellar fat pad volume on MRI, but statistical significance was lost after adjustment for IL-17 [36]. Ishibashi et al. did not find statistically significant associations between (s) adiponectin and MRI detected effusion or synovitis in a 225 knee OA participants [39]. In the current study, we have shown a statistically significant negative association between (s) adiponectin and osteophytes size on MRI in the adjusted model. There was an association between (s) adiponectin and synovitis in univariable analysis, which was lost after adjustment. This concurs with a possible protective role of adiponectin, albeit further validation studies are required. We noted a borderline association between adiponectin and WOMAC pain that was revealed only after confounder adjustment. For this, caution in interpretation should be exercised in light of a lack of statistical power. Conflicting results from literature revealed positive correlations [40,41] and null association between synovial fluid adiponectin and pain were reported [42,43].

Alissa et al. found higher levels of (s) resistin among women with knee OA compared to age-matched healthy women, and (s) resistin was positively correlated with CRP and WOMAC index among those with knee OA [12]. Data from 172 patients with severe knee OA listed for knee replacement surgery, higher (s) leptin, (s) adiponectin and (s) resistin were noted compared to healthy control who had no radiographic knee OA. Among those who had undergone surgery, (s) resistin was associated with synovial tissue inflammation on histology [44]. Our study demonstrates a negative association between (s) resistin and osteophyte size on MRI compared to a positive relationship demonstrated in existing literature. Large-scale studies are clearly warranted for verification.

We found that (s) hs-CRP was positively associated with osteophyte size and meniscus extrusion on MRI. This corroborates with other studies that showed positive association of (s) hs-CRP with pain in knee OA after adjusting for major confounders factors such as age and BMI [45,46]. The positive association between (s) hs-CRP is relevant. Meniscus extrusion is a common feature of knee OA and meniscus extrusion was found to be associated with more rapid progression of knee OA [47,48].

Several studies have reported associations between adipokines and pain. This observation is more notable for adipokines in synovial fluid [12,40,41,49] than in serum [43,50] implying that adipokines may have been released locally and then contribute to inflammation at the tissue level. This concurs with our finding of a significant association between adiponectin with WOMAC pain and function, but null for other adipokines in the adjusted models. Simultaneous evaluation of synovial fluid adipokines may give more insight to role of adipokines at a tissue level versus the systemic level. However, very few participants with earlier stage of knee OA had joint effusion. After a few previous experiments [20,25] we had inadequate directly aspirated synovial fluid samples for adipokines measurement and meaningful analysis.

Excess of fat has long been recognized as an important risk factor for OA [3,4]. Apart from the obvious biomechanical loading from the weight, bio-metabolic effects have been suggested with the observation of association of obesity with risk of OA of non-weight bearing joint such as hands [5]. In a prospective study over a 6-year period, Yusuf et al. have demonstrated the association of worsening of joint space narrowing on knee radiography and resistin, although no association with radiographic progression was seen with leptin and adiponectin [51]. Till date, the mechanisms that link adipokines to the pathogenesis of OA remain elusive [52]. It has been demonstrated that leptin stimulates the synthesis of insulin-like growth factor (IGF-1) and transforming growth factor- β (TGF-B) which could exert anabolic effects on cartilage metabolism [53]. Leptin also has roles in both innate and adaptive immunity including proliferation and activating phagocytosis of macrophages, activation of natural killer cells, and upregulates the secretion of proinflammatory cytokines such as TNFα and IL-6 [54,55]. Other immunomodulating effects or direct catabolic or anabolic effects of various adipokines have been hypothesized to mediate the pathogenesis of OA. However, no therapeutic target in regulating adipokines is available in knee OA. Further research is still needed to understand the role of each of the adipokines in the development and progression of OA.

The strength of this study is that it recruited participants with relatively earlier stage of knee OA, as compared to studies that recruited participants based on radiography which would indicate chronicity and damage. All participants had clinically diagnosed knee OA with other diagnosis excluded clinically by the attending rheumatologist. 62% of participants had MRI features which fulfilled criteria for minimal degenerative changes, affirming the validity of knee OA among participants. We used knee MRI to assess severity which can demonstrate pathological changes in all joint tissues including cartilage, infrapatellar synovitis, effusion size, meniscus, and bone marrow during the earlier stages of the disease. Thus, this cohort represents a unique opportunity to reveal the association of adipokines with MRI features. We also acknowledge several limitations in this study. The key limitation is the cross-sectional study design renders it impossible to determine a causal relationship between adipokines and OA disease progression. Further longitudinal studies of this cohort that have already been planned would help to determine the role of studied adipokines in OA disease progression. The sample size of the study is not large, thus further large-scale studies are needed to validate our findings. In this pilot evaluation, we only considered adjustment with three major variables (age, sex, BMI), confounding effects from other factors such as pain, comorbidities were not explored. We did not correct for multiple testing with multiple outcomes which may increase risk of type I errors. We acknowledge that while adipokines were measured in the systemic circulation, MRI was performed on the index knee. MRI severity of the contralateral knee was not adjusted in the models. We explored the association between adipokines with the KL sum score that may better represent disease burden of both knees but were null after adjustment. Other limitations include that, although reasonable ICC were obtained from various MRI features, the reliability of infrapatellar synovitis and effusion size were relatively low which may have an impact on the results.

5. Conclusion

In summary, in this cross-sectional study of participants with earlier stage of knee OA we demonstrated adipokines, particularly serum leptin

was associated with severity of various MRI and radiographic defects of the knee joint beyond age, sex and BMI.

Author contributions

YYL conceptualized and designed the study. JRT, CAM, SBW, and YYL acquired the data. TKYC and YYL performed the data analysis. TKYC and YYL drafted the manuscript. All authors interpreted the data, critically revised the manuscript, and approved the final version of manuscript.

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Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ocarto.2023.100405.

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