Demographic/characteristic	Placebo (n = 234)	S201086/GLPG1972 75 mg (n = 234)	S201086/GLPG1972 150 mg (n = 231)	S201086/GLPG1972 300 mg (n = 232)
Age (years), mean (SD)	63.3 (7.1)	62.9 (7.5)	63.2 (7.2)	62.1 (7.4)
Age (years), n (%)	-			
40-55	28 (12.0)	31 (13.2)	29 (12.6)	33 (14.2)
55-65	95 (40.6)	94 (40.2)	96 (41.6)	97 (41.6)
≥ 65	111 (47.4)	109 (46.6)	106 (45.9)	103 (44.2)
Women, n (%)	163 (69.7)	164 (70.1)	165 (71.4)	154 (66.1)
Race, n (%)				
White	171 (73.1)	167 (71.4)	177 (76.6)	168 (72.1)
Black or African American	25 (10.7)	27 (11.5)	19 (8.2)	25 (10.7)
Asian	32 (13.7)	31 (13.2)	28 (12.1)	30 (12.9)
American Indian, native Alaskan, or native Hawaiian or other Pacific Islander	0	1 (0.4)	1 (0.4)	2 (0.9)
Multiple	6 (2.6)	8 (3.4)	6 (2.6)	8 (3.4)
Time since first diagnosis (years), mean (SD)	7.3 (6.7)	6.9 (6.4)	7.6 (7.4)	7.1 (7.2)
KL grade, n (%)				
2	29 (12.4)	15 (6.4)	30 (13.0)	29 (12.4)
3	205 (87.6)	219 (93.6)	200 (86.6)	204 (87.6)
4	0	0	1 (0.4)	0
OARSI atlas JSN grade, n (%)				
0	0	1 (0.4)	1 (0.4)	0
1	70 (29.9)	74 (31.6)	73 (31.6)	84 (36.1)
2	164 (70.1)	159 (67.9)	156 (67.5)	148 (63.5)
3	0	0	1 (0.4)	1 (0.4)
Cartilage thickness in cMTFC, mean (SD)	3.19 (0.82)	3.25 (0.76)	3.23 (0.76)	3.33 (0.80)
Joint space width, mean (SD)	2.48 (0.86)	2.5 (0.78)	2.5 (0.78)	2.58 (0.84)

cMTFC, central medial femorotibial compartment; JSN, joint space narrowing; KL, Kellgren-Lawrence; SD, standard deviation.

Table 1 Baseline patient demographics and characteristics.

Events, n (%)	Placebo (n = 234)	S201086/GLPG1972 75 mg (n = 234)	S201086/GLPG1972 150 mg (n = 231)	S201086/GLPG1972 300 mg (n = 232)
TEAEs	174 (74.4)	174 (74.4)	177 (76.6)	174 (75.0)
Severe TEAEs	29 (12.4)	25 (10.7)	27 (11.7)	30 (12.9)
Treatment-related TEAEs	37 (15.8)	36 (15.4)	30 (13.0)	47 (20.3)
Serious TEAEs	18 (7.7)	17 (7.3)	17 (7.4)	18 (7.8)
Serious treatment-related TEAEs	2 (0.9)	0	2 (0.9)	1 (0.4)
TEAEs leading to drug withdrawal	9 (3.8)	16 (6.8)	17 (7.4)	20 (8.6)
TEAEs occurring in ≥ 5% of patients				
Arthralgia	19 (8.1)	27 (11.5	35 (15.2)	26 (11.2)
Nasopharyngitis	20 (8.5)	21 (9.0)	16 (6.9)	22 (9.5)
Fall	13 (5.6)	15 (6.4)	20 (8.7)	16 (6.9)
Back pain	19 (8.1)	11 (4.7)	10 (4.3)	7 (3.0)
Headache	9 (3.8)	15 (6.4)	12 (5.2)	11 (4.7)
Hypertension	16 (6.8)	6 (2.6)	9 (3.9)	12 (5.2)
Osteoarthritis	10 (4.3)	8 (3.4)	12 (5.2)	11 (4.7)
Increased blood creatine phosphokinase	8 (3.4)	12 (5.1)	7 (3.0)	9 (3.9)
Upper respiratory tract infection	10 (4.3)	7 (3.0)	12 (5.2)	6 (2.6)
Increased gamma-glutamyltransferase	4 (1.7)	3 (1.3)	2 (0.9)	16 (6.9)

TEAE, treatment-emergent adverse event.

Table 2 Summary of safety outcomes.

PRESENTATION NUMBER: 319

MUSCULOSKELETAL AND BIOMECHANICAL CHARACTERISTICS ARE BETTER ASSOCIATED WITH KNEE CLINICAL CONDITION THAN RADIOGRAPHIC SEVERITY IN OSTEOARTHRITIS PATIENTS

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Purpose: The diagnosis of knee osteoarthritis (OA) is typically well established with a clinical evaluation and confirmed with an X-Ray

assessing the joint' structural changes and disease progression. Guidelines also recommend taking into account mechanical factors (static and dynamic) to better understand knee function, since they may influence treatment outcomes. However, the relationship between clinical condition of the knee and biomechanical characteristics is not well known, including how such information stands compared to those from other conventional assessments, such as X-ray and physical assessment. The aim of this study is to evaluate the associations between the knee clinical condition assessed by patient-reported outcome measures and parameters from three different types of assessments, namely radiographic, musculoskeletal, and biomechanical assessment in OA patients.

Methods: This cross-sectional study was conducted on patients with 1) knee pain $\geq$ 4/10 on a numeric rating scale in the past 7 days, 2) Kellgren-Lawrence (KL) radiographic OA severity grade higher than KL2, and 3) who were not on a waiting list for knee arthroplasty. Patients' knee clinical condition was assessed using the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire that consists of five subscales: pain, symptoms, function in daily living (ADL), function in sport and recreation (Sport/Rec) and knee-related quality of life (QOL). Twenty musculoskeletal tests were performed by a therapist, including passive flexion and extension ranges of motion (ROM), muscle strength (10 tests assessing hip, knee, and ankle), flexibility (4 tests), swelling measured by the circumference difference between knees, effusion, balance, and functional 30-second chair stand tests (30s_CST). Finally, dynamic mechanical factors were measured during a knee kinesiography exam with the KneeKG™ system (Emovi Inc., QC, Canada) where 70 biomechanical parameters were extracted from 3D knee kinematic curves captured during gait (namely in flexion/extension, adduction/abduction, internal/external tibial rotation). KOOS associations with radiographic severity grades, musculoskeletal tests, and biomechanical parameters were assessed using a canonical correlation analysis (CCA). CCA is a statistical multivariate method for determining the association between two sets of variables measured on the same patients. This method is a multivariate extension of the bivariate approach, where the Pearson's correlation coefficient *r* is calculated to quantify the association between two variables. CCA consists of maximizing the Pearson's coefficient between two sets of variables. This allows calculating two distinct types of correlations: the canonical correlations (i.e. ρ coefficients) which quantify the global association between the two sets, and the structural correlations (i.e. *Corr* coefficients) which estimate the association between a set as a whole and each variable of the other set. This method was used to calculate ρ and *Corr* coefficients between the KOOS set (i.e. the scores on its five subscales) and all three other data sets (i.e. KL grades, musculoskeletal tests, biomechanical parameters). These coefficients were calculated considering all participants and also sub-groups dividing men and women to assess the impact of sex.

Results: 415 participants (251 women and 164 men) were included in this study. The mean (±standard deviation) age and body mass index were 63.3±9.2 years and 30.3±5.6 kg/m^2 respectively. The radiographic severity grade was well distributed among patients in the cohort (mild_KL2_n=137, moderate_KL3_n=149, and severe_KL4_n=129). All ρ and *Corr* coefficients presented indicate a statistically significant correlation (all $p<0.05$). Canonical correlation coefficients ρ between the KOOS set and all three other data sets are presented in Table 1. Results show that the association between KOOS and radiographic severity grades was the weakest regardless of the sample considered (both sexes combined and separated; all $\rho \leq 0.23$). Correlation coefficients were higher between KOOS and both musculoskeletal and biomechanical data for all samples (all $\rho \geq 0.38$). For women, the strongest association with KOOS was with the biomechanical parameters ($\rho=0.50$). For men, the association with KOOS was similar with the musculoskeletal tests results and the biomechanical parameters ($\rho=0.57$ and $\rho=0.55$ respectively). Structural correlation coefficients *Corr* between the KOOS set and each variable from all three other data sets (i.e. 1 ordinal KL grade, 20 musculoskeletal tests, 70 biomechanical parameters = 91 variables) when including all participants are summarized in Figure 1. For clarity purpose, only variables from the musculoskeletal and biomechanical sets which were better associated with KOOS than the radiographic severity grade are presented. Table 2 summarize the strongest correlations (absolute coefficients |*Corr*|≥0.30) between the KOOS set and each variable from all three other data sets for men and women separately. When including all participants, 5 musculoskeletal and 8 biomechanical parameters were better associated with KOOS than the radiographic severity grade (Figure 1). The result on the 30s_CST was the parameter best associated with KOOS (*Corr=0.52)*. Higher KOOS was mostly associated with greater performance on this functional test (i.e. most sit-to-stand repetitions in 30 seconds). This was also the case with greater passive ROM (i.e. "flex_ROM") and dynamic flexion ROM (i.e. during loading and end of push-off), and a smaller varus angle at the end of the push-off phase (all |*Corr*|>0.30). When separating by sex, four of these five parameters were also among the most associated with KOOS in women (Table 2). The remaining parameter (passive flexion ROM) was the second most associated with KOOS for men (after the 30s_CST), followed by a biomechanical parameter (flexion angle ROM during loading) and two additional musculoskeletal parameters (i.e. ankle plantar flexion and hip extension strengths; Table 2). Among these best-associated parameters, the 30s_CST and the flexion angle ROM during loading were the only ones shared between men and women sub-groups. Notably, the radiographic severity grade was more associated with KOOS in men than in women (*Corr*=-0.261 vs -0.161 respectively).

Conclusions: Results suggest that musculoskeletal and biomechanical characteristics are better associated with the patient clinical condition than radiographic severity for knee OA patients. Differences were observed between sexes, as women's condition was more associated with biomechanical parameters, while men's condition was similarly associated with musculoskeletal tests results and biomechanical parameters. However, similarities like the performance on the 30s_CST and the role of flexion angle ROM during loading were reported. This study supports the value of adding a biomechanical assessment to the musculoskeletal examination to better understand the clinical state of the knee and to prioritize which mechanical factors to be addressed to improve patient's condition.

Table 1. ρ coefficients between the KOOS set and all three other data sets for all participants and by sex-subgroups.

Sample considered	KOOS & Severity grades	KOOS & Musculoskeletal tests	KOOS & Biomechanical parameters
All patients	ρ=0.20	ρ=0.40	ρ=0.41
Women	ρ=0.14	ρ=0.38	ρ=0.50
Men	ρ=0.23	ρ=0.57	ρ=0.55

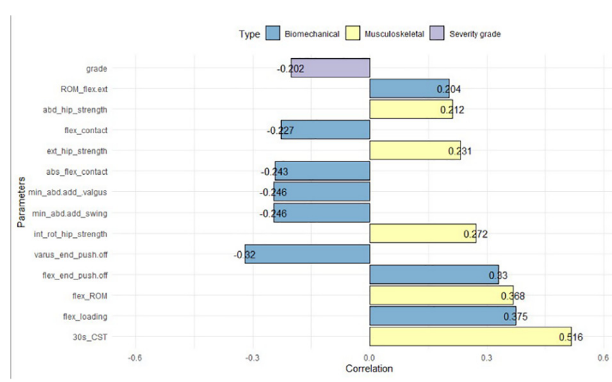

Figure 1. *Corr* coefficients between the KOOS set and each variable from all three other data sets when including all participants.

Table 2. The strongest correlations between the KOOS set and each variable from all three other data sets for men and women separately.

Parameters	Corr	Set-type
WOMEN		
varus_end_push.off	- 0.383	Biomechanical
flex_loading	0.363	Biomechanical
flex_end_push.off	0.353	Biomechanical
abd_hip_strength	0.343	Musculoskeletal
30s_CST	0.335	Musculoskeletal
Min_abd.add_swing	- 0.314	Biomechanical
Min_abd.add_valgus	- 0.314	Biomechanical
⋮	⋮	⋮
grade	- 0.161	Severity grade
MEN		
30s_CST	0.517	Musculoskeletal
flex_ROM	0.410	Musculoskeletal
flex_loading	0.367	Biomechanical
plantar_ankle_strength	0.327	Musculoskeletal
ext_hip_strength	0.303	Musculoskeletal
⋮	⋮	⋮
grade	- 0.261	Severity grade

PRESENTATION NUMBER: 320

TOPICAL CHINESE PATENT MEDICINE FOR KNEE OSTEOARTHRITIS PAIN

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Purpose: Topical non-steroidal anti-inflammatory drugs (NSAIDs) are currently strongly recommended for individuals with osteoarthritis (OA), according to 2019 American College of Rheumatology Guideline. However, topical Chinese Patent Medicine (CPM), which has been widely used to improve clinical symptoms for OA in eastern countries is less defined. A comprehensive review of the literature is an important step for understanding its benefits for OA. We systematically reviewed the literature on the clinical efficacy of topical CPM in patients with knee OA to inform clinical practice.

Methods: We performed a comprehensive search on PubMed, Cochrane Library, EMBASE and four universal Chinese databases (Biomedical Databases, National Knowledge Infrastructure, Wanfang, and Chongqing VIP) and reference lists of published articles through July 2020. Knee OA was confirmed by the American College of Rheumatology criteria or the Chinese orthopedic association criteria in all studies. We included only randomized controlled trials (RCTs) using topical CPM as the first-line treatment in adults with knee OA. To determine the effect of topical CPM on clinical symptoms, we extracted the Visual Analogue Scale (VAS, range 0-10) and the Western Ontario and McMaster Universities Arthritis Index pain scores (WOMAC pain, range 0-20), where a lower score indicates a better outcome. We also accepted the composite outcome criteria developed by the Chinese National Institute of Rheumatology as an endpoint (total effectiveness rate, range 0-100%, higher score = better outcome), which assesses the overall pain, physical function and wellness. Study quality was assessed in RevMan5.3 software using the Cochrane Risk of Bias Tool. The differences between treatment groups were reported as mean change (P-value).

Results: We identified 541 potentially relevant studies. Twenty with a total of 2395 subjects (60% female, mean age = 59 years, mean pain duration = 6 years) met eligibility criteria. Table 1 summarized the included RCTs of analgesic topical CPM on pain and function measures (VAS, WOMAC scale and Total Effectiveness Rate). All studies were conducted in China and published between 2010 and 2020. The mean treatment duration was 13 days (range 5-60 days). For the treatment groups, six topical CPM were prescribed as the first-line treatment for pain treatment based on the syndrome differentiation, and administration for once/2 days to three times a day for 5 days-8 weeks. The control group treatments included oral NSAIDs (10 studies), topical NSAIDs (7 studies), sodium hyaluronate (1 study), off-loading brace (1 study) and hot compress (1 study). Overall quality of trials was modest. Nine studies showed significantly improved VAS pain scores compared to control groups (Mean Difference [MD] = 0.74; 95% confidence interval, 0.60 to 0.88; $p<0.01$). Two studies showed significantly improved WOMAC pain scores compared to control ($p=0.02$). Seven studies reported a significant improvement in overall clinical symptoms on both pain and function ($p<0.01$). Minor adverse events (rash, pruritus, swelling and anaphylases) were reported in the both treatment groups.

Conclusions: This study suggested that Chinese topical CPM is safe and has potential benefits in knee pain relief compared to standard medications. Further rigorously designed studies are warranted to understand the analgesic effect, anti-inflammatory effect and the activation of blood circulation indicated in Chinese medicine for patients with knee OA.

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Author, year	N[a]	Age[b]	Topical CPM (Formula, Dose)[c]	Control Intervention	Duration (wks)	Outcome Measures	Effect on Symptom(Mean or Percentage Improvement)[d]	P value
Zhao, 2008	60	64	Fufang Nanxing Zhitong plaster, once/2 days, for 24 hours at a time, 6 times	Voltaren emulsion, 3 times/day, 12 days	2	WOMAC pain	1.33 ↓	< 0.05
Yu,2009	120	53	Xiaotongtie plaster, once/day,24 hours at a time, 8 wks	Celecoxib tablets, 100 mg, twice/ day, 8 wks	8	WOMAC Pain	0.59 ↓	< 0.01
Hu, 2011	60	62	Xiaotongtie plaster, once/day, 24 hours at a time, 2 wks	Celecoxib capsules, 200 mg, once/ day, 2 wks	2	Chinese composite outcome	Treatment effect: ↑90% vs. 86.6%	> 0.05
Xu, 2011	100	NR	Xiaotongtie plaster, once/day, 24 hours at a time, 1 wk	Meloxicam tablets, 7.5 mg, twice/ day, 1wk	1	VAS pain	0.46 ↓	< 0.05
Guo, 2011	180	59	Xiaotongtie plaster, once/day, 24 hours at a time, 15 days	Diclofenac tablets,75 mg, twice/day, 15 days	2	Chinese composite outcome	Treatment effect: ↑91.9% vs. 78.0%	< 0.05
Wang, 2011	80	53	Xiaotongtie plaster, once/day, 6 hours at a time, 1 wk	Dielofenac tablets, 25 mg, twice/ day, 1 wk	1	VAS pain	1.35 ↓	< 0.01
Zhang, 2011	60	55	Xiaotongtie plaster, once/day, 24 hours at a time, 4 wks	Diclofenac tablets, 75 mg, 1-2 times/day, 4 wks	4	Chinese composite outcome	Treatment effect: ↑93% vs.56%	< 0.01
Lv,2011	160	60	Xiaotongtie plaster, once/day, 24 hours at a time, 5 times	Diclofenac tablets, 100 mg, once/ day, 5 days	1	VAS pain	1.5 ↓	< 0.01
Lu, 2011	62	65	Xiaotongtie plaster, once/day, 24 hours at a time, 7 days	Diclofenac tablets, 25 mg, 3 times/ day, 7 days	1	Chinese composite outcome	Treatment effect: ↑86.67% vs. 84.38%	> 0.05

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