Soluble intercellular adhesion molecule-1: a potential biomarker for pain intensity in chronic pain patients

Aim: Pain therapy is strongly guided by patients' self-reporting. However, when self-reporting is not an option, pain assessment becomes a challenge and may lead to undertreatment of painful conditions. Pain is a complex and multifactorial phenomenon. Recent work has connected pain pathophysiology also with the inflammatory system. We therefore hypothesized that pain intensity could be predicted by cytokine-levels. **Patients & methods:** In this observational, single-center study, we investigated 30 serum cytokines to predict pain intensity in a screening/follow-up set of 95 chronic pain patients and controls. We then prospectively validated soluble intercellular adhesion molecule-1 (sICAM-1)'s discriminatory capability ($n = 21$). **Results & conclusion:** sICAM-1 was significantly associated with patient-reported pain intensity and yielded differential serum levels in patients of varying degrees of pain intensity. Changes in pain ratings over time correlated with changes in sICAM-1 levels. Our findings suggest the possibility of a clinical use of sICAM-1 as a potential biomarker for pain intensity.

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Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” [1]. For thousands of years, people have produced and used analgesic agents, such as herbal extracts, opium and alcohol, in order to make pain more tolerable. Despite the long history of successful treatment of pain, diagnostic measures still mainly rely on patients' self-reporting and unspecific clinical features such as overall appearance, heart-rate and blood pressure. Consequently, pain therapy becomes a guessing game, when a patient is unable to reliably self-report her or his pain [2]. It has been estimated that the prevalence of undertreated pain may be as high as 80% in older adults in long term care facilities and patients with severe dementia [3,4]. Moreover, several studies

have demonstrated that pain is experienced by the overwhelming majority of intubated patients in intensive care units [5]. In these patients, poor pain management is accompanied by prolonged length of stay, duration of mechanical ventilation, increased rates of nosocomial infections and the development of chronic pain and post-traumatic stress disorder [6,7]. Therefore, the lack of nonverbal avenues to measure pain impacts patients' well-being and healthcare costs greatly [5–7].

Pain is a highly complex and poorly understood phenomenon that is heavily influenced by psychosocial factors [8] and subjective experience, but also by a huge variety of cellular mechanisms [9]. Recent studies have linked inflammatory molecules to pain pathophysiology [10–15]. These studies, however, did not focus on the identification of a surrogate

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marker for pain intensity. Hence, we hypothesized that pain might be assessable to some extent by inflammatory molecules measurable in serum. In the current study, we therefore investigated a panel of 30 pro- and anti-inflammatory markers in chronic pain patients and healthy controls. We identified soluble intercellular adhesion molecule-1 (sICAM-1) to be the serum marker most strongly associated with pain intensity. We derived a serum cut-off level yielding acceptable sensitivity and specificity, and prospectively confirmed these findings with follow-up data and a set of newly recruited patients and healthy controls.

Materials & methods

Study design & population

The study followed the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Ludwig Maximilians University of Munich. Written informed consent was obtained from all participants. The study was designed as an observational, case-control, single center study to assess predictive capability of 30 cytokines to predict pain intensity levels. Chronic pain patients and healthy controls fulfilling the inclusion criteria were recruited within 18 months, starting 9/2011 (screening set). Patients available to follow-up after 6 months were re-analyzed to assess internal validity (follow-up set). While all of these patients had received treatment, there was no specific intervention for this study and pain treatment covered a broad range such as medication, physical therapy and psychological techniques. After identification of sICAM-1 as a potential surrogate marker of pain intensity, we prospectively recruited 15 new patients and six healthy control subjects to validate our results (validation set). All patients of at least 18 years of age visiting the Department of Anesthesiology and Pain Medicine, University Hospital of Munich for chronic pain, were considered eligible to participate in this study. Exclusion criteria were a recently started medication with opioids, nonopioids or co-analgesics, treatment or prior history of treatment with immunomodulatory agents, any signs of chronic or acute inflammatory disease (such as fever, abnormal total or differential leukocyte count, and increased plasma-concentration of C-reactive protein), autoimmune, neoplastic, or psychiatric disease, drug abuse, pregnancy, and a major impairment of renal or liver function (for patient flow diagram see Figure 1). Reassessment of exclusion criteria was performed at the day of blood sampling. In order to avoid bias introduced by the type of pain, patients with neuropathic, nociceptive and mixed pain as well as patients with complex regional pain syndrome were included.

Pain syndromes

Nonspecific chronic low back pain (CLBP) was defined as persistent low back pain not attributable to a recognizable specific pathology (e.g., infection, tumor, osteoporosis, trauma, inflammatory disorder or radicular syndrome). Diagnosis of a complex regional pain syndrome I was made when a patient met the 'Budapest Criteria' and suffered from unilateral symptoms in a limb [16]. Patients with other types of chronic pain included polyneuropathy, postherpetic neuralgia, orofacial pain, mixed pain and musculoskeletal pain.

Assessment of pain intensity & stress

Patients rated their current pain intensity at rest and movement at the time point of blood sampling using an 11-point numeric rating scale (NRS), ranging from 'no pain' (0) to 'worst pain imaginable' (10). The maximum of these two was then selected. Mild pain was defined as the range 0–3, moderate pain as 4–6 and severe pain as 7–10 points. This classification was based on the distribution of pain intensity scores of patients declaring that the pain was unbearable to them (minimum NRS = 3, median NRS = 6, maximum NRS = 10). Self-perceived stress was evaluated using the German version of the Questionnaire for Actual Demands ('KAB': 'Kurzfragebogen zur aktuellen Beanspruchung'). The KAB was designed to repeatedly quantify an individual's acute or chronic distress. It is highly sensitive to short-term or situational changes during a stressful experience. The rating is based on a 6-point scale ranging from 1 to 6 based on normalized adjectives. Higher KAB values (rating scale, 1–6) indicate increased perceived levels of distress [17].

Determination of cytokines

Blood samples were collected, centrifuged and stored in polypropylene aliquot tubes at -80°C until examination. Serum levels of 30 pro- and anti-inflammatory cytokines were measured by Myriad Rules-Based Medicine, (Texas, USA), using the Human Cytokine multiplex immunoassay (Human Cytokine Map A+B). The multiplex microbead assay is based on Luminex technology and measures proteins in a similar manner to standard sandwich ELISA, with comparable sensitivity and range [18,19]. Measurements below the limit of detection were set to 50% of the detection limit. Cytokines were excluded from subsequent analysis, when the great majority of measurements were below the limit of detection.

Statistics

We used the open source statistical software R for statistical analysis. Using a random simulation model,

Figure 1. Patient flow diagram.

we estimated the required sample size for detection of a biomarker at a power between 50% (standard deviation 10% of the mean) and 90% (standard deviation 5% of the mean) to be $n = 70$ patients and 23.3 healthy controls (see [Supplementary File 1](#)). Initial analyses had been carried out on the screening set (first recruitment period); results were tested on a follow-up set and an unseen validation set (second recruitment period), whose size was determined by the observed effect size in the screening cohort. The ratio of 1:3 (healthy control:pain patients) was maintained. We used a three-step analysis approach: correlation analysis between sICAM-1 and raw NRS values, predictive analysis of raw cytokine levels and categorized pain levels (no, mild, medium, severe), and binarized sICAM-1 and pain levels (no/mild vs medium to severe pain) to evaluate clinical usefulness. Comparisons between two groups were performed using the Mann–Whitney U test. We tested for a non-normal distribution via the Kolmogorov–Smirnov test. For multigroup comparisons, the Kruskal–Wallis test was used. The resulting p-values were adjusted to control for a false discovery rate of 5% based on the

Benjamini–Hochberg algorithm. If significant, the Mann–Whitney U test was used as a post hoc test. Correlation was assessed using Pearson’s product-moment correlation and resulting p-values were corrected to control for a maximum false discovery rate of 5% (q-values are reported). Throughout the manuscript, a significance level of $p < 0.05$ was set. All markers were evaluated in terms of expression differences between control (no pain), mild, moderate and severe pain. Predictive potential of the remaining candidate cytokines was evaluated in terms of significance in discriminatory power of a univariate logistic regression model to discern patients from healthy controls, healthy controls and patients with mild pain versus patients with moderate and severe pain, and patients with mild versus those with moderate and severe pain. Calibration was evaluated by calculating Hosmer–Lemeshow’s goodness-of-fit statistic for $g = 5, 10$ and 15 groups. In order to assess the relation between changes in pain intensity and biomarker values, the relative change was calculated. Confounding was assessed by testing the impact of gender, age, pain type, level of education, body mass index, history of coronary heart disease, total

cholesterol, high- and low density lipoprotein, smoking, renal function (measured by glomerular filtration rate and creatinine serum levels), conflict of interest and prior pain medication on the estimated sICAM-1 effect in a logistic regression model. Additionally, the structure of a Bayesian network was learned using the bnlearn package (Figure 2; for detailed description see Supplementary File 1). Effect modification was evaluated by assessing the significance of the interaction term with the median-binarized variable. Conflict of

interest was defined as immediate and obvious personal or financial benefit for the patient, if the condition persists. Level of education was coded as '1': no school degree, '2': high school degree without additional training, '3': high school degree with additional training, '4': college degree, '5': university degree. Propensity scores were matched using nearest-neighbor matching. After matching, scores were tested for normality and a paired *t*-test was performed to avoid significant differences in propensity score distribution ($p > 0.9$).

Figure 2. The automatically inferred structure of a Bayesian network. According to this network, the effect of pain intensity on sICAM-1 levels might be confounded by level of education (via cholesterol and HDL).

GFR: Glomerular filtration rate; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; NSAID: Nonsteroidal anti-inflammatory drug; sICAM-1: Soluble intercellular adhesion molecule-1.

Results

Study design & population

A total of 457 new patients visited our pain department in the recruitment period of 18 months. Of these, 383 were not included because of exclusion criteria, while the remaining 74 patients were considered eligible for our study. Three of these patients were excluded after eligibility assessment, but prior to blood sampling because of symptoms of an acute infection during physical exam. Twenty-four healthy subjects devoid of acute or chronic pain were recruited in parallel. The resulting screening cohort included 35 men of age 21–83 years and 60 women of age 20–77 years. Of these 71 chronic pain patients, 53 patients were available for follow-up measurements 6 months after the initial assessment (Table 1). After identification of sICAM-1 as a potential surrogate marker of pain intensity, we prospectively recruited 15 new patients and six healthy control subjects. The validation cohort consisted of five men of age 26–66 years and 16 women of age 19–78 years.

Identification of candidate markers

Eight of 30 cytokines measured were below detection limits. Therefore, we analyzed serum levels of the 22 detectable cytokines in 71 patients suffering from mild to severe pain and 24 healthy control subjects.

Of these molecules, IL-6 and sICAM-1 showed differential serum levels between patients with mild and patients with moderate or severe pain (Figure 3A & Table 2). sICAM-1 was the only candidate that yielded significant correlation between the self-reported pain level and measured serum levels in patients (correlation $r = 0.43$; 95% CI: 0.22–0.61; $q < 0.001$).

Development of a biomarker panel

We grouped study subjects into those with no (controls) and mild versus those with moderate and severe pain in order to design a biomarker panel based on a logistic regression model. Using penalized stepwise logistic regression, the model contained sICAM-1, IL-6, IL-23 as covariate predictors in order to discern healthy controls from patients, as well as to distinguish no or mild pain from moderate to severe pain (Table 3). Only sICAM-1 remained to discriminate between mild versus moderate and severe pain. Since a significant amount of IL-6 measurements were below the limit of detection, we also defined a model of IL-6 levels and a binary variable indicating if IL-6 levels were measurable. This model revealed that measurability is more predictive of pain than IL-6 levels themselves. Univariate models based on sICAM-1 to predict pain intensity appear to be well

Table 1. Patient demographics.

Variable	Screening set	Follow-up set	Validation set
Total number	95	53	21
Patients:			
– Number	71	53	15
– Age (years)	47 (20–83)	47 (21–77)	58 (19–78)
– Gender	48:23 (F:M)	34:19 (F:M)	13:2 (F:M)
– Level of education	3 (1–5)	3 (2–5)	3.5 (1–5)
– Smoking	20	16	3
– Pain intensity	5 (0–10)	5 (0–10)	8 (2–10)
– Pain types:			
– CLBP	40	37	2
– CRPS	9	2	6
– Other	22	14	7
Control subjects:			
– Number	24	0	6
– Age (years)	41 (23–55)	NA	31 (26–45)
– Gender	12:12 (F:M)	NA	3:3 (F:M)
– Level of education	4.5 (3–5)	NA	4.5 (2–5)
– Smoking	2	NA	0
Data presented as median (range). CLBP: Chronic low back pain; CRPS: Complex regional pain syndrome; F:M: Female:male; NA: Not applicable; Other: Other types of chronic pain syndromes; where applicable, values are reported as median (range).

Figure 3. Evaluation of sICAM-1 as a potential pain predictor (see facing page). (A) Comparison of sICAM-1 to IL-6 in the screening and follow-up set. Values were normalized to the median expression of the healthy control subjects. For IL-6, only values above the limit of detection were considered for calculating the median expression. (B) AUC for sICAM-1 in order to discriminate: healthy controls from patients; healthy controls and patients with mild pain from patients with moderate and severe pain; and patients with mild from patients with moderate to severe pain. The color-coded, shaded areas correspond to the 95% CIs. (C) Relative changes of sICAM-1 correlate with relative changes in pain intensity. The dotted lines represent the 95% CI of the regression line. (D) AUCs for different pain types; shaded areas represent the 95% CIs for each receiver-operating-characteristic (E) Self-reported pain intensity versus sICAM-1 levels show significant correlation. (F) Clinical markers of pain for no or mild pain (o) and moderate to severe pain (+). Values are normalized to the respective median value of the no or mild pain group.

AUC: Areas under the receiver-operating-curve; CLBP: Chronic lower back pain; CRPS: Complex regional pain syndrome; KAB: Kurzfragebogen zur aktuellen Beanspruchung; MAP: Mean arterial pressure; sICAM-1: Soluble intercellular adhesion molecule-1.

calibrated (p : 0.11–0.72), yielding AUCs of 0.85 and 0.79 (Figure 3B).

Derivation & evaluation of an sICAM-1 cut-off

sICAM-1 serum levels were normally distributed in the control group. We therefore defined a cut-off value one standard deviation from the mean, resulting in 112.8 ng/ml. Sensitivity and specificity were calculated for the full screening set, the reduced screening set including patients only, the follow-up set and the validation set consisting of patients and control subjects. Sensitivity ranged from 0.77 (follow-up set) to 1.0 (validation set) and specificity from 0.57 (follow-up set) to 1.0 (validation set; see Supplementary File 1, Supplementary Table 2). We estimated the odds ratio for identifying moderate to severe pain to be 11.65 (95% CI: 3.80–41.67). This was based on the aforementioned cut-off value in the full screening set from a logistic regression model. The model was adjusted for level of education, cholesterol and high-density lipoprotein, as a result of the confounder analysis (see ‘Assessment of Confounding’).

Reevaluation & correlation analysis between sICAM-1 & pain intensity changes

In order to assess internal validity, sICAM-1 levels were remeasured in 53 patients from the screening set that were available for follow-up analysis after conservative therapy. Both, the univariate models as well as the combined model of sICAM-1 and IL-6 were evaluated on these data, yielding similar results as in the screening cohort (Figure 3A). We also assessed the association between changes in pain and changes in sICAM-1 values (Figure 3C). Overall, there was a medium correlation between changes in self-reported pain and changes in sICAM-1 serum levels ($r = 0.33$; $q = 0.03$). We then investigated patients with and without a potential conflict of interest separately, as it might affect the reported pain intensity. Stratification yielded a similar correlation for patients without conflict of interest ($r = 0.37$; $n = 39$; $q = 0.03$), and no significant correlation for patients with conflict ($r = 0.15$; $n = 14$; $q = 0.63$).

Analysis of subsets

We subgrouped patients in our study into patients with chronic low back pain, complex regional pain syndrome and other types of pain (mostly neuropathic). These diseases are assumed to have different underlying mechanisms of pathology. We therefore investigated, if there were substantial differences in the discriminative power of sICAM-1 based on pain syndromes, revealing a lower AUC in patients with chronic low back pain than in other types of pain (CLBP: 0.78 [0.65–0.90], complex regional pain syndrome: 0.98 [0.95–1.00], other pain: 0.95 [0.89–1.00]). However, we found great overlap in the 95% CIs of the ROC curves (Figure 3D). Figure 3E illustrates pain levels versus sICAM-1 serum levels, suggesting a positive relationship between pain and sICAM-1 for all subgroups.

Assessment of confounding

Since sICAM-1 levels have been associated with cardiovascular risk, inflammation, diabetes and obesity, we first tested a set of potentially confounding variables for significant differences in distribution between healthy controls and patients [20–23]. Healthy control subjects had less prior pain medication, were younger with a higher level of education and were less likely smokers. When stratifying for pain intensity, smokers showed an insignificant tendency toward lower sICAM-1 values. Next, we investigated all variables in a multivariate logistic regression model to evaluate their impact on the estimated effect of sICAM-1 (Table 4). None of the variables affected the estimated sICAM-1-effect (0.06; 95% CI: 0.05–0.09 in the univariate model) significantly. Smoking, HbA_{1c}, level of education and conflict of interest significantly contributed to the model. Level of education impacted the estimated sICAM-1 effect the most. We furthermore learned the structure of a Bayesian belief network to investigate more complex structural relationships between variables (see Figure 2). In accordance with the multivariate modeling, the network structure suggests that level of education may serve as a potential confounder, since it influences pain intensity as well as sICAM-1 levels (via cholesterol

Table 2. Inter-group comparison of soluble intercellular adhesion molecule-1 and IL-6[†]

Pain Level	IL-6 [‡]	sICAM-1
Control vs mild pain	0.8 vs 0.8 (p = 0.58)	101.5 vs 104 (p = 0.72)
Mild vs moderate pain	0.8 vs 2.4 (p = 0.01)	104 vs 124.5 (p = 0.009)
– Moderate pain vs control	-2.4 vs 0.8 (p = 0.004)	-124.5 vs 101.5 (p < 0.001)
Moderate vs severe pain	2.4 vs 2.6 (p = 0.65)	124.5 vs 150 (p = 0.03)
– Severe vs mild pain	-2.6 vs 0.8 (p = 0.02)	-150 vs 104 (p < 0.001)
– Severe pain vs control	-2.6 vs 0.8 (p = 0.006)	-150 vs 101.5 (p < 0.001)

[†]Median value group 1 vs median value group 2 (p-value).
[‡]Values below the limit of detection (1.6 ng/ml) were set to 50% (0.8 ng/ml).
sICAM-1: soluble intercellular adhesion molecule-1.

and high-density lipoprotein). We then built a propensity score matching model on these variables on patients with mild, and patients with moderate to severe pain (see [Supplementary Figure 2](#)). The estimated AUC on a propensity-score matched cohort (n = 12 mild pain and n = 12 moderate to severe pain) was 0.76 (95% CI: 0.56–0.95). Effect modification was tested by the introduction and evaluation of interaction terms. None of the tested variables displayed significant effect modification.

Comparison to clinical markers

We evaluated the clinical parameters heart rate and mean arterial blood pressure which may help to estimate the pain intensity of patients who are not able to report it themselves. Even though heart rate and mean arterial pressure showed an increased median value in patients with moderate to severe pain, the difference was not significant. Assessment of distress measured by serum cortisol levels and a psychological questionnaire for assessment of current distress revealed no significantly different cortisol levels, but significantly higher KAB scores in moderate to severe pain ([Figure 3F](#)). In linear and logistic regression modeling, KAB scores did not significantly contribute to sICAM-1 serum lev-

els in predicting pain intensity in patients, while it did significantly enhance discrimination between patients and controls (see [Supplementary File 1](#)).

Discussion

Despite a plethora of technological advances in modern medicine, measurement of pain is still limited to a patient's ability to self-report or judgment of clinical parameters such as heart rate and blood pressure. Recent literature suggests a crosstalk between pain and inflammation [13–15]. Therefore, we investigated a set of 30 inflammation- and pain-related biomarkers to search for potential capability as a biomarker of pain. We found that sICAM-1 measured in serum correlates with patients' self-reported pain levels and, interestingly, could reliably discern between patients with no or mild pain and patients suffering from moderate to severe pain. In predictive modeling, sICAM-1 outperformed clinical parameters such as heart rate and mean arterial pressure. We estimated sensitivity and specificity at sICAM-1 serum levels of 112.8 ng/ml to be 0.83 and 0.76, respectively. Discriminatory potency was similar among patients with chronic low back pain, complex regional pain syndrome and patients with

Table 3. Inter-group comparison of three potential biomarkers.[†]

Model	sICAM-1		IL-6		IL-23	
	AUC (95% CI)	Coefficient (95% CI)	AUC (95% CI)	Coefficient (95% CI)	AUC (95% CI)	Coefficient (95% CI)
Univariate:						
– Control + patients	0.85 (0.77–0.93)	0.06** (0.04–0.09)	0.72 (0.62–0.81)	0.66** (0.29–1.10)	0.61 (0.50–0.73)	1.14* (0.09–2.28)
– Patients only	0.79 (0.66–0.92)	0.04** (0.02–0.07)	0.72 (0.57–0.86)	0.57* (0.10–1.22)	0.49 (0.34–0.64)	-0.048 (-1.46–1.39)
Multivariate:						
– Control + patients	0.89 (0.82–0.95)	0.050** (0.02–0.08)	0.89 (0.82–0.95)	0.75** (0.24–1.37)	0.89 (0.82–0.95)	1.88* (0.36–3.57)

*p < 0.05.
**p < 0.01.
AUC: Area under the receiver operator characteristic; sICAM-1: soluble intercellular adhesion molecule-1.

Table 4. Assessment of confounding.[†]

Variable		sICAM-1	Interaction
Name	p-value	Coefficient	p-value
Coronary heart disease	0.86	0.060	0.99
Smoking**	0.007	0.059	0.82
Arterial hypertension	0.35	0.060	0.80
Gender	0.46	0.058	0.48
Conflict of interest*	0.03	0.060	0.41
Medication with NSAIDs	0.51	0.061	0.93
Medication with opioids	0.99	0.059	>0.99
Medication with alkaline drugs	0.99	0.056	>0.99
Age	0.07	0.056	0.64
Body mass index	0.54	0.056	0.63
Level of education*	0.03	0.049	0.76
HbA _{1c} *	0.04	0.063	0.75
Creatinine	0.91	0.060	0.60
Total cholesterol	0.72	0.059	0.88
Low density lipoprotein	0.74	0.057	0.39
High density lipoprotein	0.09	0.062	0.67

[†]Parameters estimated from a multivariate model on the full screening set; sICAM-1 coefficient 95% CI: 0.04–0.09.

*/**Parameter significantly contributed to the multivariate model (* $p < 0.05$; ** $p < 0.01$).

HbA_{1c}: Glycosylated hemoglobin A1C; NSAID: Nonsteroidal anti-inflammatory drug; sICAM: soluble intercellular adhesion molecule-1.

other types of pain. Additionally, changes in sICAM-1 levels correlated with changes in pain intensity. We tested a variety of variables for potential confounding or effect modification, using different strategies, such as model adjustment, propensity scores and stratification.

sICAM-1 is mainly expressed on the endothelial cell surface. It serves as a counter-receptor for the lymphocyte function-associated antigen (LFA-1) and facilitates leukocyte adhesion and endothelial transmigration [24]. Its soluble form, sICAM-1 was first described in a clinical setting in the early 1990s, when discussed in the context of diabetes, cardiovascular and inflammatory diseases [20]. In the following years, it has gained attraction as a biomarker for pancreatitis, obesity and obstructive sleep apnea, subarachnoid hemorrhage, hepatocellular carcinoma, and endothelial dysfunction or infectious diseases and sepsis [21,23,25–29]. None of these studies – some of which investigated in extremely painful conditions – stratified for pain levels. Importantly, some studies already reported elevated sICAM-1 levels in cluster headache, inflammatory and neuropathic pain, and painful bladder syndrome, underlining a role in painful diseases [30–32].

Various cytokines as well as other circulating molecules such as miRNA have been investigated for several pain conditions. In mouse, Kusuda *et al.* found that miRNAs are differentially expressed in the spinal cord

under different pain conditions [33]. In CLBP patients, a recent work reported the predictive implication for therapy response for miRNA hsa-miR-124 [34]. However, none of these studies established a potential biomarker for pain intensity. Sun *et al.* found that serum levels of the proinflammatory cytokine IL-15 are positively associated with pain intensity in patient suffering from knee osteoarthritis [14]. In the discussion, the authors point out that the observed correlation rather refers to a potential role of IL-15 in the pathogenesis of osteoarthritis-related pain than in pain perception *per se*. Koch *et al.* investigated a range of inflammatory cytokines and nitric oxide in plasma of chronic pain patients. They found that only IL-6 levels and nitric oxide were significantly enhanced in all, light, moderate and severe pain states compared with pain-free controls [15]. However, these markers were not able to reliably discern between the groups with no, mild, moderate and severe pain. In accordance with these results, IL-6 was also found to be elevated in chronic pain patients in our study. However, the present investigation is the first to show that sICAM-1 levels correlate with self-reported pain intensity across different chronic pain syndromes, and may allow clinicians to distinguish between patients with no or mild pain from patients with moderate to severe pain. The current study does not allow us to draw inferences on the nature of the relationship between sICAM-1

and pain. Serum levels may not necessarily reflect the sensation of pain, but may be the result of a secondary process, as is the case with other routinely used clinical surrogate markers. A previous work of Machelska *et al.* described sICAM-1 as a key molecule involved in the recruitment of opioid-containing leukocytes [35]. Additionally, Rutkowski *et al.* found sICAM-1 to be involved in pain mediation in rats with induced lumbar radiculopathy [36]. In this context, sICAM-1 serum levels might reflect the body's reaction to a painful stimulus.

There is general consensus that chronic pain is also intimately linked to psychosocial factors like anxiety, depression and catastrophizing. Therefore, we assessed the relationship between sICAM-1 and surrogate markers of distress such as serum cortisol and self-perceived stress (KAB). While cortisol levels were not predictive of pain, the KAB score correlated with pain intensity. In a multivariate logistic regression model, the KAB score added significant information in discerning patients from control subjects. However, analysis within patients revealed that KAB values did not significantly contribute to the prediction of pain intensity in linear or logistic regression when sICAM-1 values are known. In summary, our interpretation of these findings is that sICAM-1 levels seem to reflect the sensory-discriminative component of pain rather than the affective one.

At this point, it is not clear if our results are extendable to acute pain or patients in other facilities. Furthermore, clinical utility in the context of comorbidities remains to be evaluated. Before a possible clinical utility can be established, it will be necessary to reproduce our findings in independent cohorts with different study designs. Another limitation of our study is the significant difference of demographic variables among groups.

Conclusion

Pain is a complex and multifactorial phenomenon including biological, psychological and social aspects. Nevertheless, based on the results presented in this manuscript, we believe that sICAM-1 has the potential to serve as a biomarker predicting a painful condition that needs intervention when patients are unable to reliably self-report their pain.

Supplementary data

To view the supplementary data that accompany this paper, please visit the journal website at: www.future-science.com/doi/full/10.2217/bmm-2016-0246

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The study followed the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Ludwig Maximilians University of Munich. Written informed consent was obtained from all participants.

Summary points

- Since pain assessment is difficult when patients' self-reporting is not an option, this study aimed to identify a potential biomarker to help guiding clinicians.
- Using a panel of 30 serum measurable cytokines, soluble intercellular adhesion molecule-1 (sICAM-1) significantly correlated with patients' self-reported pain levels.
- Changes in sICAM-1 levels correlated with changes in pain levels on follow-up.
- In predictive modeling sICAM-1 yielded good sensitivity and specificity.
- Using a sICAM-1 cutoff of 112 ng/ml a validation cohort could be perfectly separated into healthy controls and chronic pain patients.
- Clinical utility would be greatest in geriatric and Intensive Care Unit patients, who are many times unable to reliably self-report their pain levels.

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