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C-Reactive Protein and Pain Sensitivity: Findings from Female Twins

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Abstract

Background—Systemic inflammation and pain sensitivity may contribute to the development and maintenance of chronic pain conditions.

Purpose—We examined the relationship between systemic inflammation as measured by C-reactive protein (CRP), and cold pain sensitivity in 198 female twins from the University of Washington Twin Registry. We also explored the potential role of familial factors in this relationship.

Methods—Linear regression modeling with generalized estimating equations examined the overall and within-pair associations.

Results—Higher levels of CRP were associated with higher pain sensitivity ratings at pain threshold ($p = 0.02$) and tolerance ($p = 0.03$) after adjusting for age, body mass index, time to reach pain threshold or tolerance, and clinical pain status. The magnitude of the associations remained the same in within-pair analyses controlling for familial factors.

Conclusions—The link between CRP and pain sensitivity may be due to non-shared environmental factors. CRP and pain sensitivity can be examined as potential biomarkers for chronic pain and other inflammatory conditions.

Keywords

C-reactive Protein; Pain Sensitivity; Environment; Genetics; Chronic pain

INTRODUCTION

Chronic pain is a major health concern that accounts for 80% of physician visits as well as increases in disability and morbidity (1). In order to minimize and possibly prevent the

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Conflict of Interest Statement

None of the authors have any conflicts of interest to declare.

development of chronic pain, it is important to examine potential predictive factors and their mechanisms of action. Two factors that appear to be at the nexus of chronic pain development and maintenance are inflammation and pain sensitivity.

Inflammation is assessed by measuring circulating levels of inflammatory markers, such as interleukin (IL)-6, IL-1, tumor necrosis factor (TNF)- α , and C-reactive protein (CRP) (2). CRP is an especially useful marker of systemic inflammation that has been linked to conditions such as cardiovascular disease, diabetes, osteoporosis, asthma, diabetes, and myocardial infarction (3). While high sensitivity-CRP (hs-CRP) levels over 10 mg/L reflect clinically significant inflammation, subclinical levels of 3 – 10 mg/L suggest an elevated risk for the development of disease (4). For example, subclinical levels of hs-CRP have been associated with psychosocial stress, unhealthy behaviors, and sleep problems in relatively healthy populations [4]. Of relevance to chronic pain, small increases in hs-CRP levels have been linked to the development of a number of pain conditions, including rheumatoid arthritis and fibromyalgia (3,4).

Pain sensitivity also has been related to the development and maintenance of chronic pain. Pain sensitivity is generally conceptualized in terms of pain *threshold*, the smallest stimulus intensity in which pain is detected by an individual; pain *tolerance*, the maximum pain intensity an individual is willing to stand; and ratings of painfulness at threshold and tolerance. Increases in pain sensitivity have been associated with several chronic pain conditions such as fibromyalgia (5) and low back pain (6). Further, a study of participants diagnosed with whiplash injuries found non-recovery to be related to decreased pain tolerance (7). A prospective cohort study found that individuals with higher levels of pain sensitivity had a higher incidence rate of temporomandibular disorders (8). These findings suggest that pain sensitivity may serve as a marker for subsequent development of chronic pain.

Although previous investigations suggest that systemic inflammation as measured by hs-CRP and pain sensitivity may contribute to the development and maintenance of chronic pain conditions, no studies have examined the potential link between hs-CRP and pain sensitivity. The primary aim of this study was to determine if there is a relationship between levels of hs-CRP and cold pain sensitivity in female twins. Because data were collected in twins, an additional aim was to elucidate the potential role of familial factors in this relationship.

METHODS

Participants

The Twin Study of Chronic Widespread Pain was an investigation of the psychological, behavioral, and physiological risk factors for and correlates of medically unexplained chronic pain in women. Female twins were selected from the University of Washington Twin Registry, which is a community-based registry of twins identified through the Washington State Department of Licensing. The characteristics of the Twin Registry have been reported elsewhere (9).

Study participants were 198 twins (99 twin pairs) from the Registry, all of whom lived in Washington State or Oregon. Pairs were recruited between 2006 and 2010. Given the study's focus on medically unexplained chronic pain, both twins had to be free from severe or chronic medical conditions that are typically associated with or give rise to chronic pain (e.g. autoimmune disorders, cancer, etc.), or other medical conditions that could interfere with the study measurements, including cardiopulmonary disorders, uncontrolled endocrine conditions, and uncontrolled allergic or sleep disorders. Potential participants also were

excluded if they were current smokers, tested positive for drugs of abuse during the study visit, had body mass index of < 20 or $> 30 \text{ kg/m}^2$, were pregnant or planning to become pregnant during the course of the study, had an amputated limb, or were completely blind or deaf. Potential participants who were either pain-free or had chronic pain not related to a known disease or organic etiology and did not meet the above exclusionary criteria were eligible to participate. Participants were asked to discontinue all medications that affect sleep, hypothalamic-pituitary-adrenal axis function, or autonomic nervous system functioning for two weeks prior to and during the study evaluation. In addition, all pain medications were discontinued for the duration of the study. The study protocol allowed participants to take short-acting over-the-counter pain relievers (e.g., Tylenol) as needed. However, none of the participants needed to take pain relievers during the 2-day laboratory visit. Alcohol (2 drinks per week) and caffeine (1 cup of coffee per day) were also restricted for the duration of the study.

Once enrolled, twin pairs completed a 7-day at-home salivary cortisol protocol, kept a daily diary of sleep, stress, mood, and pain levels, and completed a comprehensive battery of questionnaires. Immediately after the at-home protocol, the twin pairs presented for a 2-day visit at the University of Washington General Clinical Research Center, where they had a comprehensive history and physical examination; engaged in laboratory, pain sensitivity, and exercise testing; and underwent holter monitoring. Twins came to the Research Center together but were evaluated separately at each step. Written informed consent was obtained from all participants and the study was approved by the Institutional Review Boards at the University of Washington and University of California, San Diego.

The participants were all female with an average age of 29 years ($SD = 10$); 89% identified themselves as White and 92% had some college education or greater. The twins had an average body mass index (BMI) of 23.5 kg/m^2 .

Measures

Sociodemographic information included age, race and ethnicity, education level, and marital status. Weight and height were used to calculate BMI. Pain status was obtained during a pre-visit telephone interview. The cold pressor test for pain sensitivity was conducted during the first day of the laboratory visit. Phlebotomy for hs-CRP was performed in the afternoon of the first Research Center day prior to pain testing.

Clinical Pain Status

Pain status was determined using the London Fibromyalgia Study Screening Questionnaire, a validated screening tool that assesses for continuous pain in muscles, bones, or joints, above and below the waist, and in the head, neck, spine or back in the past three months (10). Information from this instrument was used to categorize twins' pain status. Localized pain was defined as continuous pain in one region, regional pain as continuous pain in 2 regions, and widespread pain was defined as continuous pain in 3 or more regions. The regional and widespread pain groups were collapsed into a single category for analyses.

C-Reactive Protein

Levels of hs-CRP were established via nephelometry (Beckman SYNCHRON® System) with a threshold of 0.2 mg/L and intra- and inter-assay coefficients of less than 2.3% and 3.1%, respectively. For analysis, hs-CRP levels were dichotomized as $\leq 3 \text{ mg/L}$ or $> 3 \text{ mg/L}$ in accordance with the Centers for Disease Control and Prevention and the American Heart Association guidelines (11).

Evoked Pain Sensitivity

Pain sensitivity was assessed by a cold pressor test in which a container was filled with water that was kept at approximately 1–2°C through the use of ice cubes and a submerged pump. Each participant was asked to place her non-dominant hand and forearm in the water compartment for no longer than 5 minutes, and to indicate when the sensation changed from cold to pain (threshold) and when the participant could no longer stand the pain (tolerance), upon which she could withdraw her arm from the water. Participants also were instructed to rate their overall pain level “at this moment” using a visual analog scale (VAS), anchored at “no pain” and “worst pain ever”. VAS ratings were taken immediately prior to the start of the procedure (baseline), at threshold, and at tolerance. In order to adjust for baseline pain levels, we computed pain threshold and pain tolerance difference scores by subtracting the baseline pain rating from the ratings at threshold and tolerance, respectively. Time in seconds to threshold and tolerance were used as measures of latency to threshold and tolerance. The baseline-adjusted pain ratings at threshold and tolerance were used as measures of pain sensitivity.

Statistical Analyses

Descriptive statistics were computed as means and standard deviations for continuous measures and percentages for categorical measures. We used linear or logistic regression to compare demographic and clinical characteristics according to hs-CRP level. The regression models were fit using generalized estimating equations with robust variance estimation to account for twin correlation. We used Pearson correlation coefficients to examine the association between the pain sensitivity ratings and time to pain threshold or tolerance. Inferential testing for this association used generalized estimating equations regression models to account for twin correlation.

We also used Cox regression to determine if time to pain threshold and tolerance differed according to hs-CRP level. Models were adjusted for age, BMI, and pain status; standard errors accounted for correlation within twin pair. Resulting hazard ratios compared the rate for reaching pain threshold or tolerance in twins with hs-CRP > 3mg/L to twins with hs-CRP ≤ 3mg/L. Hazard ratios > 1 indicate twins with hs-CRP > 3mg/L had a higher rate for reaching pain threshold or tolerance compared to twins with hs-CRP ≤ 3mg/L.

Our analytic approach to address the primary study aims was to first estimate the overall association between hs-CRP and pain sensitivity ratings, and then estimate the within-pair effects by comparing twins with hs-CRP of > 3mg/L to co-twins with hs-CRP of ≤ 3mg/L. Because twin pairs share a similar family environment and a portion of their genes (100% in monozygotic and on average 50% in dizygotic pairs), within-pair estimates control for familial influences. If a within-pair association is attenuated and rendered non-significant compared to the overall effect obtained in the initial regression analyses, we can conclude that familial factors contribute to that association. Alternately, a within-pair association that remains robust compared to the overall effect provides evidence that familial factors do not play a prime role in the association between hs-CRP and pain sensitivity. We used linear regression modeling with generalized estimating equations to examine the overall and within-pair association between hs-CRP and pain sensitivity. Overall models and associated means and confidence intervals were adjusted for age, BMI, time until pain threshold or tolerance was reached, and pain status. Within-pair models included the same adjustment variables except age which did not vary for twins within a pair. Significance level was set at $p < 0.05$. All data analyses were conducted using Stata 10.1 for Windows (StataCorp LP, College Station, TX).

RESULTS

Of the 198 twins who participated in the study, 2 participants (1%) were excluded due to missing hs-CRP values and 4 participants (2%) were excluded because the baseline pain rating was higher than the threshold pain rating. Table 1 presents the demographic and clinical characteristics by hs-CRP level. Age, zygosity, education, race, marital status, time until pain threshold or tolerance, and pain status did not significantly differ according to hs-CRP level. Twins with hs-CRP values $> 3\text{mg/L}$ had significantly higher BMI than those with hs-CRP values $\leq 3\text{mg/L}$.

The correlation between threshold pain sensitivity rating and time until pain threshold was -0.04 ($p = 0.54$) while the correlation between tolerance pain sensitivity rating and time until pain tolerance was -0.15 ($p = 0.10$). Results from the Cox regression models indicated that the rate at which participants reached either pain threshold (hazard ratio = 1.1; $p = 0.82$) or tolerance (hazard ratio = 1.3; $p = 0.28$) did not significantly differ in twins with hs-CRP values $> 3.0\text{ mg/L}$ compared to twins with hs-CRP $\leq 3.0\text{ mg/L}$.

The findings from the overall regression modeling indicated that hs-CRP was significantly associated with pain sensitivity ratings at threshold ($p = 0.02$) and tolerance ($p = 0.03$) after adjusting for age, BMI, time until pain threshold or tolerance, and pain status (Table 2). As expected, clinical pain status was significantly negatively related to pain sensitivity ratings at threshold and tolerance. Figure 1 shows that twins with hs-CRP values $> 3.0\text{ mg/L}$ rated their threshold pain an average of 11.2 points higher and their tolerance pain an average of 9.2 points higher than twins with hs-CRP values $\leq 3.0\text{ mg/L}$.

Nineteen twin pairs were discordant for hs-CRP level and were included in within-pair analyses (Table 3). After adjusting for familial factors, the magnitude of the associations between hs-CRP and ratings of pain at threshold and tolerance were similar to the overall associations. Twins with hs-CRP values $> 3.0\text{ mg/L}$ rated their threshold pain an average of 11.3 points higher than twins with hs-CRP values $\leq 3.0\text{ mg/L}$ ($p = 0.02$). Tolerance pain ratings were an average of 9.7 points higher in twins with hs-CRP values $> 3.0\text{ mg/L}$ compared to those with hs-CRP values $\leq 3.0\text{ mg/L}$; however, the difference was not statistically significant ($p = 0.10$).

DISCUSSION

To our knowledge, this is the first study to examine the relationship between hs-CRP and cold pain sensitivity in female twins. We found that there is a significant relationship between hs-CRP and pain ratings at threshold and tolerance. Specifically, these findings indicate that clinically important levels of hs-CRP ($> 3.0\text{ mg/L}$) in a relatively young and healthy sample is associated with greater pain sensitivity, even after controlling for age, BMI, latency to pain, and pain status.

CRP is a general index of inflammation. While CRP levels can increase within 6 hours of an acute inflammatory stimulus (e.g., infection) with similarly sharp drops after treatment, minimally or moderately increased levels are a sign of low-grade systemic inflammation. Chronically elevated levels of CRP have been associated with high blood pressure, obesity, and chronic infections such as gingivitis (11). CRP has already been identified as a marker for the development of cardiovascular disease and is associated with other medical conditions such as diabetes and rheumatoid arthritis (4). Of particular relevance to chronic pain, higher levels of hs-CRP have been found in individuals with fibromyalgia (3), and a study examining patients with rheumatoid arthritis found that hs-CRP was inversely associated with wrist pain threshold after adjusting for sleep problems and psychological distress (12). Our findings extend the existing literature to suggest that subclinical levels of

hs-CRP may be relevant to the experience of pain even in relatively healthy individuals. Given the standardized and reproducible manner in which hs-CRP values can be obtained (13), the measure shows great promise as a potential biomarker for the development of medically unexplained chronic pain. Likewise, evoked pain sensitivity has been explored as a potential biomarker for the development of chronic pain conditions (7,8). Our finding of a link between hs-CRP and cold pain sensitivity suggests that evoked pain sensitivity can be explored as a potential biomarker for other health conditions that involve inflammatory processes (14).

We also found that while the significance levels for the associations were somewhat reduced, the magnitude of the relationship between hs-CRP and cold pain sensitivity ratings remained relatively robust after controlling for shared familial factors. These findings suggest that familial factors may not play a significant role in the relationship between hs-CRP and cold pain sensitivity, and point to a potential role for non-shared environmental factors. There are several environmental factors that are related to both hs-CRP levels and pain sensitivity, and can be examined as contributors common to both increasing hs-CRP levels and increased pain sensitivity. Of particular relevance is the known impact of physical activity and cardio-respiratory fitness on both hs-CRP levels and pain sensitivity (15,16). Cardiorespiratory fitness is inversely related to hs-CRP levels (15). Intense physical exercise is associated with elevated cold pain threshold and decreased pain and unpleasantness responses to a cold pressor test (16). Psychological factors such as perceived helplessness and catastrophizing also may play a role in the link between hs-CRP and pain sensitivity, and can be examined as potential mediators of this relationship. In a clinical sample of 146 rheumatoid arthritis patients, elevated levels of hs-CRP were strongly associated with both helplessness and disease activity (17). Catastrophizing also has been associated with enhanced inflammatory responses to stress and pain (18). Future studies can further examine the role of these and other non-shared environmental or behavioral factors such as nutrient intake (19), in the link between hs-CRP and pain sensitivity.

We also found several surprisingly negative results. The correlations between pain sensitivity ratings and latency to threshold and tolerance were not significant. However, the coefficients were consistently negative for both time points, showing that twins with higher pain ratings reached pain threshold and tolerance more quickly than those with lower pain ratings. This supports the hypothesis that twins with higher pain ratings did, in fact, have increased pain sensitivity. In addition, we found that hs-CRP level was not significantly related to clinical pain status. This finding suggests that there may not be a direct unadjusted association between hs-CRP and medically unexplained chronic pain that is predominately musculoskeletal in nature. However, because of the small number of twins with localized, regional, or widespread pain, lack of power to detect a relationship cannot be ruled out. We also found that hs-CRP was not associated with latency to cold pain threshold and tolerance. These findings are consistent with a recent study of hs-CRP and pressure pain threshold in rheumatoid arthritis patients (12). Authors report that although unadjusted analyses did not reveal significant associations between hs-CRP and pressure pain threshold, multivariable analyses that adjusted for sleep problems and psychiatric distress revealed a strong inverse association between hs-CRP and wrist pain threshold. Thus, several factors such as sleep difficulties and psychiatric distress may be relevant to the relationship between hs-CRP and cold pain threshold and tolerance. Future studies should further examine the complex relationship of hs-CRP, latency to pain, and other factors in multivariate analyses.

This study has several strengths. Mainly, we examined a large sample of relatively healthy women with the exception of musculoskeletal pain. Because of the stringent health criteria, we bypassed many of the problems such as smoking status that need to be addressed in a study of CRP. Nonetheless, there are several limitations. First, the small number of twins

with medically unexplained chronic pain did not allow us to fully examine the role of hs-CRP and pain sensitivity in those who have unexplained chronic pain. Second, our assessment of pain sensitivity focused on cold pain. Therefore, our findings should be replicated with other experimental pain procedures. Third, the within-pair analyses relied on a small number of CRP-discordant twin pairs. Fourth, because of the community-based nature of the study, we were unable to confirm hs-CRP values with a second laboratory test within 2 weeks of the initial test, or to obtain another hs-CRP level on twins with hs-CRP > 10 mg/L. Although not ideal for clinical settings, our approach was consistent with other studies that have examined hs-CRP in non-clinical cohorts (20). In addition, due to the strict exclusion criteria for participation, potential participants with acute or chronic inflammatory conditions were excluded from participation. As a result, only 5 of the 192 (2.6%) study participants who were included in the analyses had an hs-CRP level > 10 mg/L. Our analysis approach categorized hs-CRP (≤ 3 vs. > 3 mg/L) which greatly reduces the impact these outliers have on the results. Finally, these cross-sectional data prevent us from determining a potentially causal relationship between hs-CRP and pain sensitivity. Clearly, a longitudinal study is necessary to better examine the nature of the association and to examine the role of these factors in the development and maintenance of medically unexplained chronic pain conditions.

In conclusion, we found that higher levels of hs-CRP were associated with higher pain ratings at threshold and tolerance in female twins. We also found that this association may be partially due to non-shared environmental factors and are not significantly influenced by shared familial factors. Our findings highlight the need to examine both hs-CRP and pain sensitivity ratings as potential biomarkers for chronic pain and other conditions that involve inflammatory processes. Future studies can examine specific environmental contributors to hs-CRP and pain sensitivity. Longitudinal studies can explore this association and its role in the development and maintenance of chronic pain conditions.

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Figure 1.

Average pain rating difference scores and 95% confidence intervals at threshold and tolerance by hs-CRP level for the overall sample of female twins

Table 1

Demographic and clinical characteristics of female twins

Characteristic	CRP $\leq$ 3.0 mg/L (n = 163)	CRP > 3.0 mg/L (n = 29)
<i>Demographic</i>		
Age, mean years (SD)	28.5 (9.5)	30.5 (11.3)
Monozygotic, %	74	79
Bachelor's degree or higher, %	50	52
White, %	87	97
Married or cohabitating, %	36	34
<i>Clinical</i>		
Body mass index *, mean kg/m ² (SD)	23.1 (3.1)	25.7 (3.9)
Time until pain threshold reached, mean sec (SD)	18.1 (18.5)	19.3 (25.2)
Time until pain tolerance reached, mean sec (SD)	67.8 (76.1)	51.1 (56.5)
Pain status, %		
None	72	66
Localized	15	28
Regional / Widespread	12	7

*
p < 0.01

Overall regression coefficient estimates for the association between hs-CRP and baseline-adjusted pain ratings at threshold and tolerance

Table 2

Independent variable	Pain threshold rating			Pain tolerance rating		
	β	(95% CI)	p-value	β	(95% CI)	p-value
hs-CRP, mg/L	11.2	(1.8, 20.5)	0.02	9.2	(0.8, 17.7)	0.03
Age, years	0.2	(-0.2, 0.5)	0.39	0.1	(-0.3, 0.4)	0.66
Body mass index, kg/m ²	-0.4	(-1.2, 0.4)	0.30	0.2	(-0.7, 1.0)	0.72
Time until pain threshold or tolerance, sec	-0.1	(-0.2, 0.1)	0.33	0.0	(-0.1, 0.1)	0.13
Pain status						
None	Reference	--	--	Reference	--	--
Localized	-6.8	(-12.9, -0.7)	0.03	-7.1	(-14.2, -0.1)	0.05
Regional / Widespread	-13.2	(-20.6, -5.9)	<0.01	-16.3	(-25.5, -7.1)	<0.01

β = change in pain rating for a one unit change in the independent variable; CI = confidence interval

Within-pair regression coefficient estimates for the association between hs-CRP and baseline-adjusted pain ratings at threshold and tolerance

Table 3

Independent variable	Pain threshold rating			Pain tolerance rating		
	β	(95% CI)	p-value	β	(95% CI)	p-value
hs-CRP, mg/L	11.3	(1.9, 20.7)	0.02	9.7	(-1.9, 21.2)	0.10
Body mass index, kg/m ²	-0.6	(-2.5, 1.2)	0.49	-0.3	(-2.1, 1.5)	0.72
Time until pain threshold or tolerance, sec	-0.1	(-0.3, 0.2)	0.48	0.0	(-0.1, 0.1)	0.99
Pain status						
None	Reference	--	--	Reference	--	--
Localized	-20.6	(-30.0, -11.2)	0.02	-13.4	(-24.6, -2.3)	0.02
Regional / Widespread	-17.2	(-33.9, -0.5)	<0.01	-21.5	(-39.4, -3.7)	0.02

β = change in pain rating for a one unit change in the independent variable; CI = confidence interval